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DELAWARE STATE MEDICAL JOURNAL

Official Organ of the Medical Society of Delaware

INCORPORATED 1789

VOLUME 30 NOVEMBER, 1958 NUMBER 11

ANEMIA

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REFERENCES: (1) Royer, A., in Welch, H., & Martí-Ibañez, F.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 783. (2) Waisbren, B. A., & Strelitzer, C. L.: *Arch. Int. Med.* **101**:397, 1958. (3) Koch, R., & Donnell, G.: *California Med.* **87**:313, 1957. (4) Roy, T. E.; Collins, A. M.; Craig, G., & Duncan, I. B. R.: *Canad. M. A. J.* **77**:844, 1957. (5) Cooper, M. L., & Keller, H. M.: *J. Dis. Child.* **95**:245, 1958. (6) Caswell, H. T., *et al.*: *Surg., Gynec. & Obst.* **106**:1, 1958. (7) Brown, J. V.; Sedwitz, J. L., & Hanner, J. M.: *U. S. Armed Forces M. J.*: **9**:161, 1958. (8) Sarason, E. L., & Bauman, S.: *Surg., Gynec. & Obst.* **105**:224, 1957.

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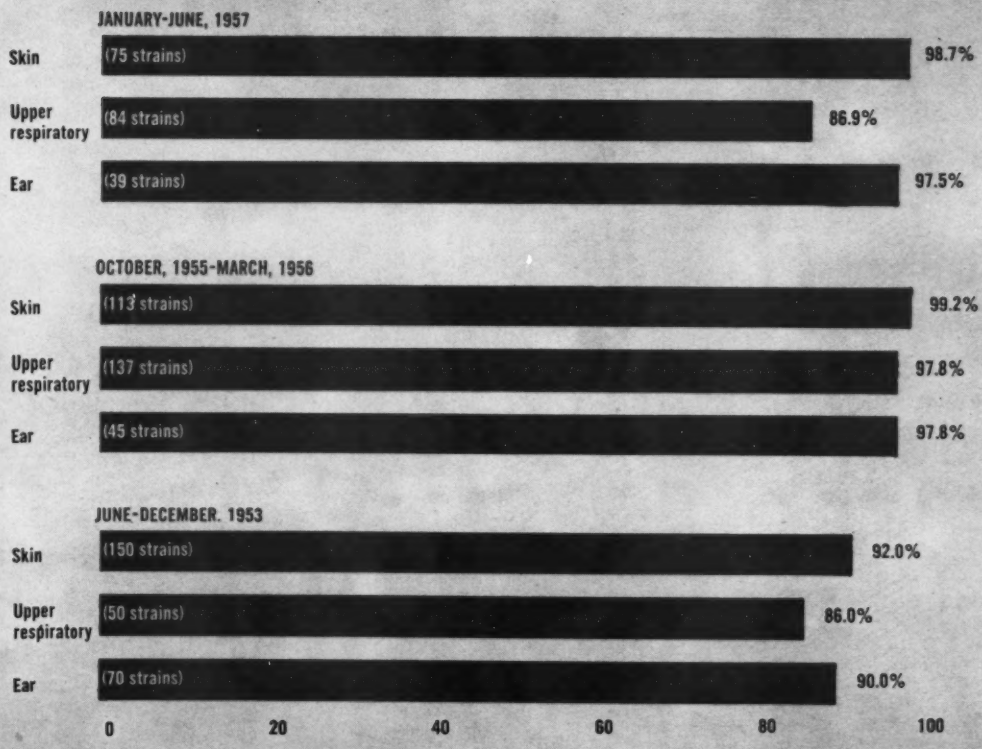

*Adapted from Royer.[1]

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(1) Hagedorn, A. B.: Proc. Staff Meet. Mayo Clin. 32:705 (Dec. 11) 1957. (2) Best, W. R.; Louis, J., and Limarzi, L. R.: M. Clin. North America (Jan.) 1958, p. 3.

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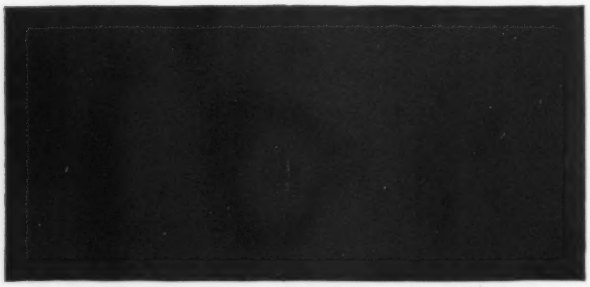

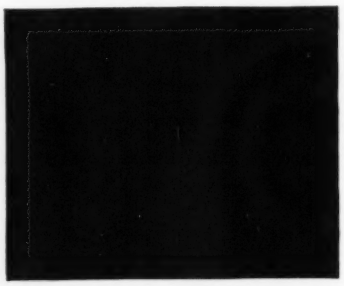

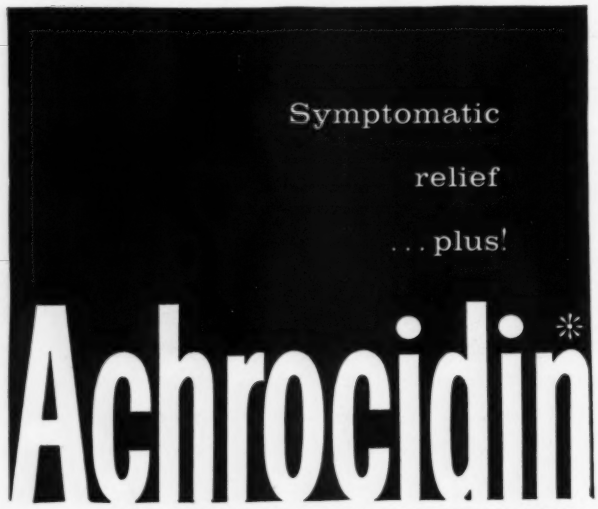

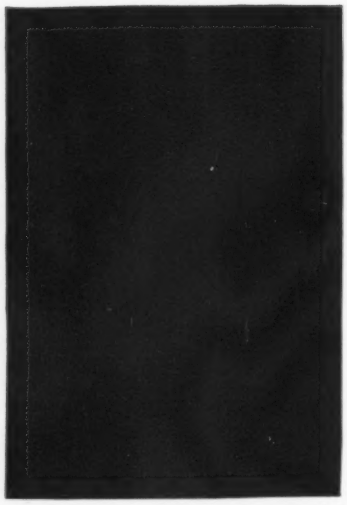

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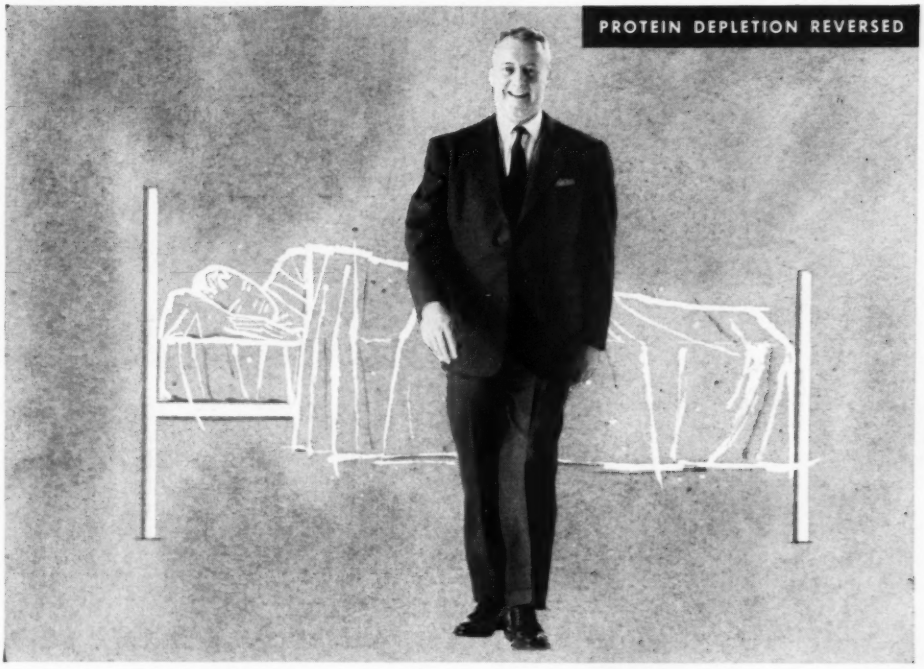

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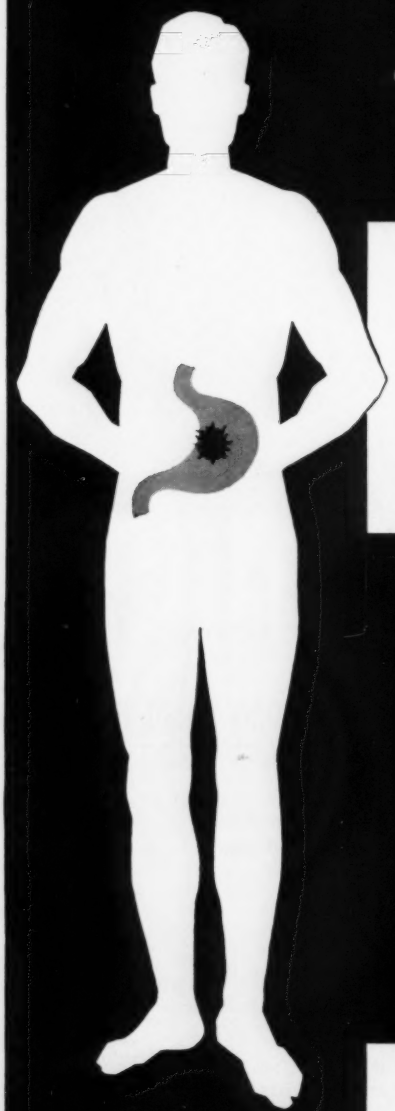

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STUDY 2[2]		"pronounced"			
Herniated disc	39	25	13	—	1
Ligamentous strains	8	4	4	—	—
Torticollis	3	3	—	—	—
Whiplash injury	3	2	1	—	—
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STUDY 3[5]		"excellent"			
Herniated disc	8	6	2	—	—
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1. *Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Card.* **1**:395, March 1958.
2. *Shapiro, S.: Observations on the use of meprobamate in cardiovascular disorders. Angiology* **8**:504, Dec. 1957.

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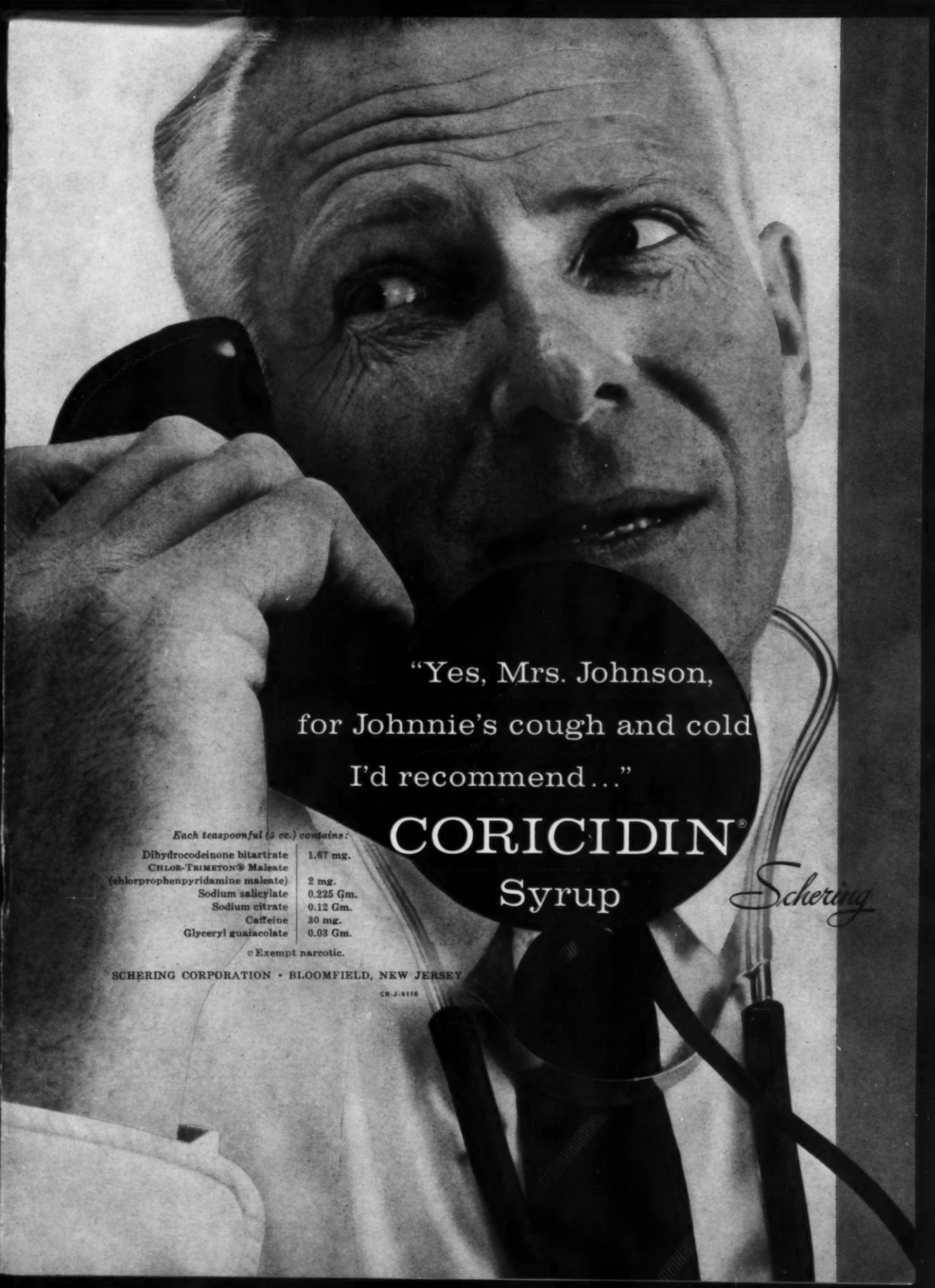
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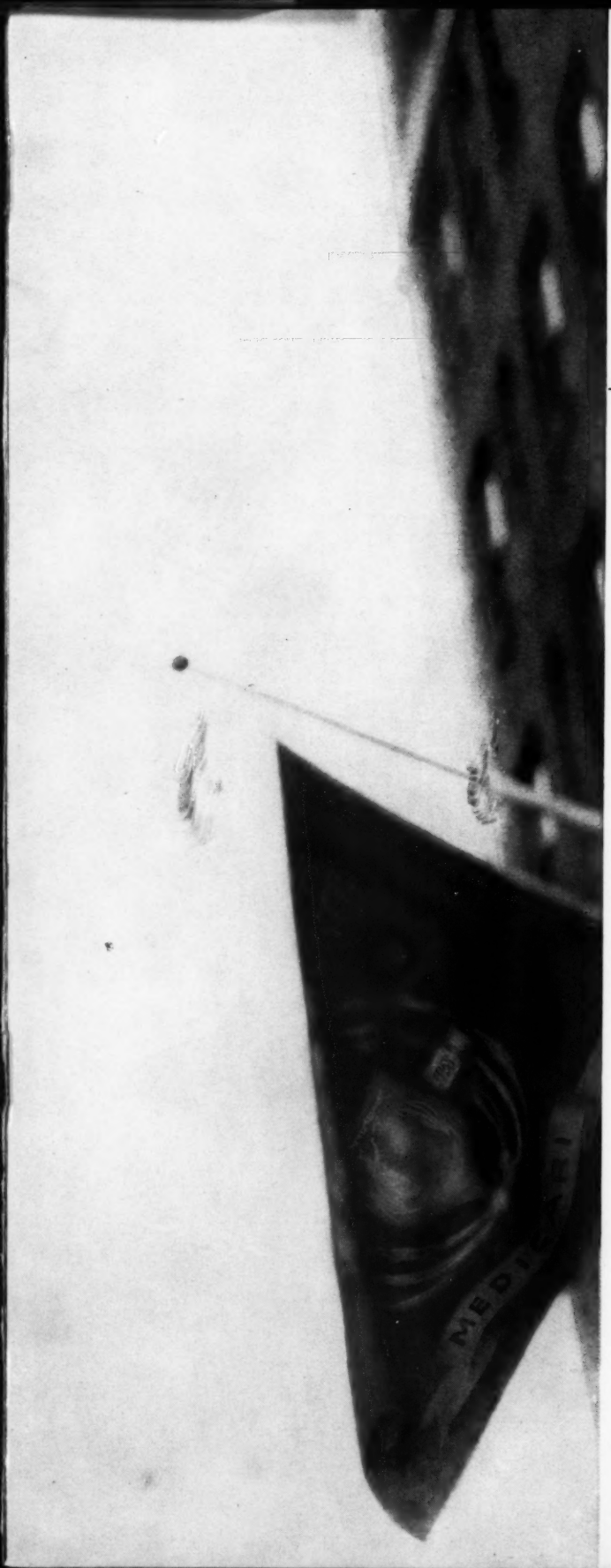

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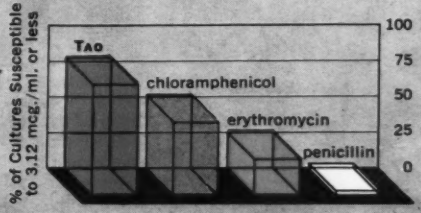
even against resistant staph[1,2]. . .

Per cent of "antibiotic-resistant" epidemic staphylococci cultures susceptible to TAO, erythromycin, penicillin and chloramphenicol.[1]



well tolerated . . .

REACTIONS:

(a) adults	(b) children
Total—9.2% (20 out of 217)	Total—0.6% (1 out of 167)
Skin rash—1.4% (3 out of 217)	Skin rash—none
Gastrointestinal—7.8% (17 out of 217)	Gastrointestinal—0.6% (1 out of 167)

There was complete freedom from adverse reactions in 94.5% of all patients. Side effects in the other 5.5% were usually mild and seldom required discontinuance of therapy.

plus . . . stability in gastric acid • rapid, high and sustained blood levels • high urinary concentrations • outstanding palatability in a liquid preparation

Dosage and Administration: Dosage varies according to the severity of the infection. For adults, the average dose is 250 mg. q.i.d.; to 500 mg. q.i.d. in more severe infections. For children 8 months to 8 years of age, a daily dose of approximately 30 mg./Kg. body weight in divided doses has been found effective. Since TAO is therapeutically stable in gastric acid, it may be administered at any time, without regard to meals.

Supplied: TAO Capsules—250 mg. and 125 mg.; bottles of 60. TAO for Oral Suspension—1.5 Gm.; 125 mg. per teaspoonful (5 cc.) when reconstituted; unusually palatable cherry flavor; 2 oz. bottle.

References: 1. English, A. R., and Fink, F. C.: Antibiotics & Chemother. (Aug.) 1958. 2. English, A. R., and McBride, T. J.: Antibiotics & Chemother. (Aug.) 1958. 3. Wennersten, J. R.: Antibiotic Med. & Clin. Therapy (Aug.) 1958. 4. Celmer, W. D., et al.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 476.

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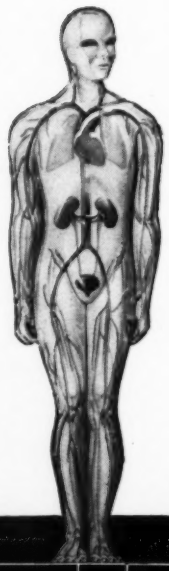
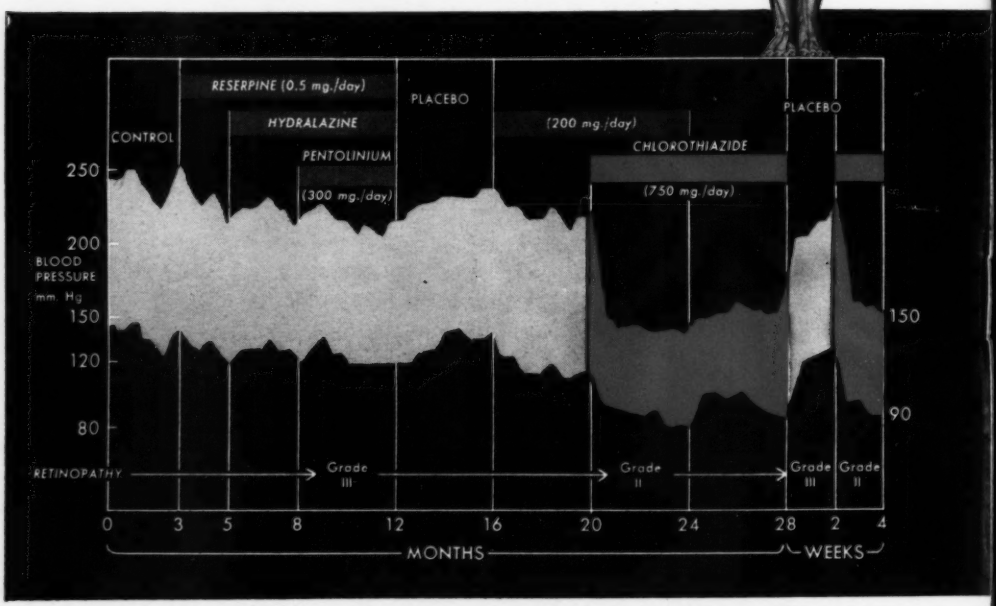
Wilkins, R. W.: New England J. Med. **257**:1026, Nov. 21, 1957.

"Chlorothiazide added to other antihypertensive drugs reduced the blood pressure in 19 of 23 hypertensive patients." "All of 11 hypertension subjects in whom splanchnicectomy had been performed had a striking blood pressure response to oral administration of chlorothiazide." ". . . it is not hypotensive in normotensive patients with congestive heart failure, in whom it is markedly diuretic; it is hypotensive in both compensated and decompensated hypertensive patients (in the former without congestive heart failure, it is not markedly diuretic, whereas in the latter in congestive heart failure, it is markedly diuretic). . . ."



Freis, E. D., Wanko, A., Wilson, I. H. and Parrish, A. E.: J.A.M.A. **166**:137, Jan. 11, 1958.

"Chlorothiazide (maintenance dose, 0.5 Gm. twice daily) added to the regimen of 73 ambulatory hypertensive patients who were receiving other antihypertensive drugs as well caused an additional reduction [16%] of blood pressure." "The advantages of chlorothiazide were (1) significant antihypertensive effect in a high percentage of patients, particularly when combined with other agents, (2) absence of significant side effects or toxicity in the dosages used, (3) absence of tolerance (at least thus far), and (4) effectiveness with simple 'rule of thumb' oral dosage schedules."



In "Chlorothiazide: A New Type of Drug for the Treatment of Arterial Hypertension,"
'Hollander, W. and Wilkins, R. W.: Boston Med. Quart. **8**: 1, September, 1957.

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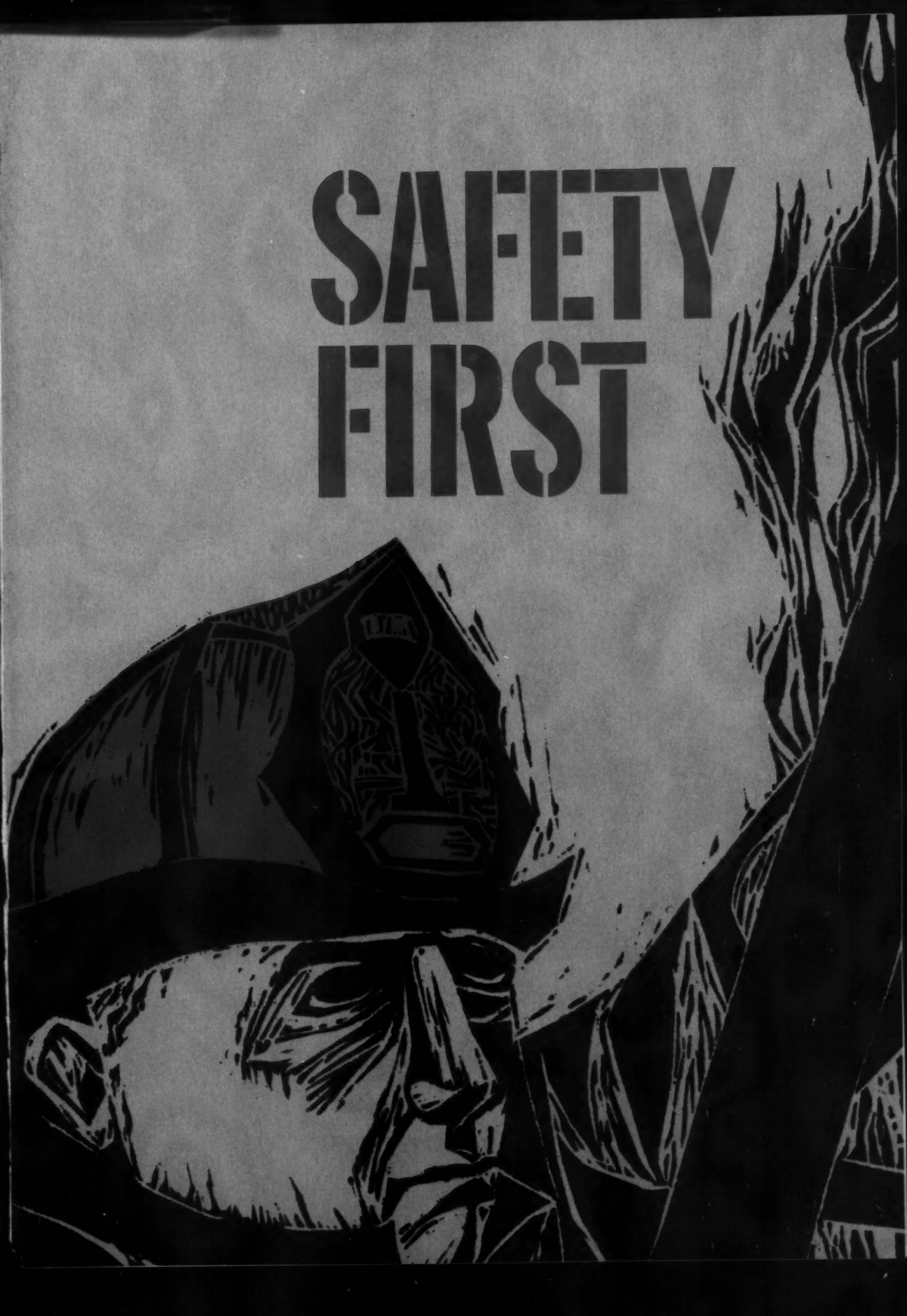
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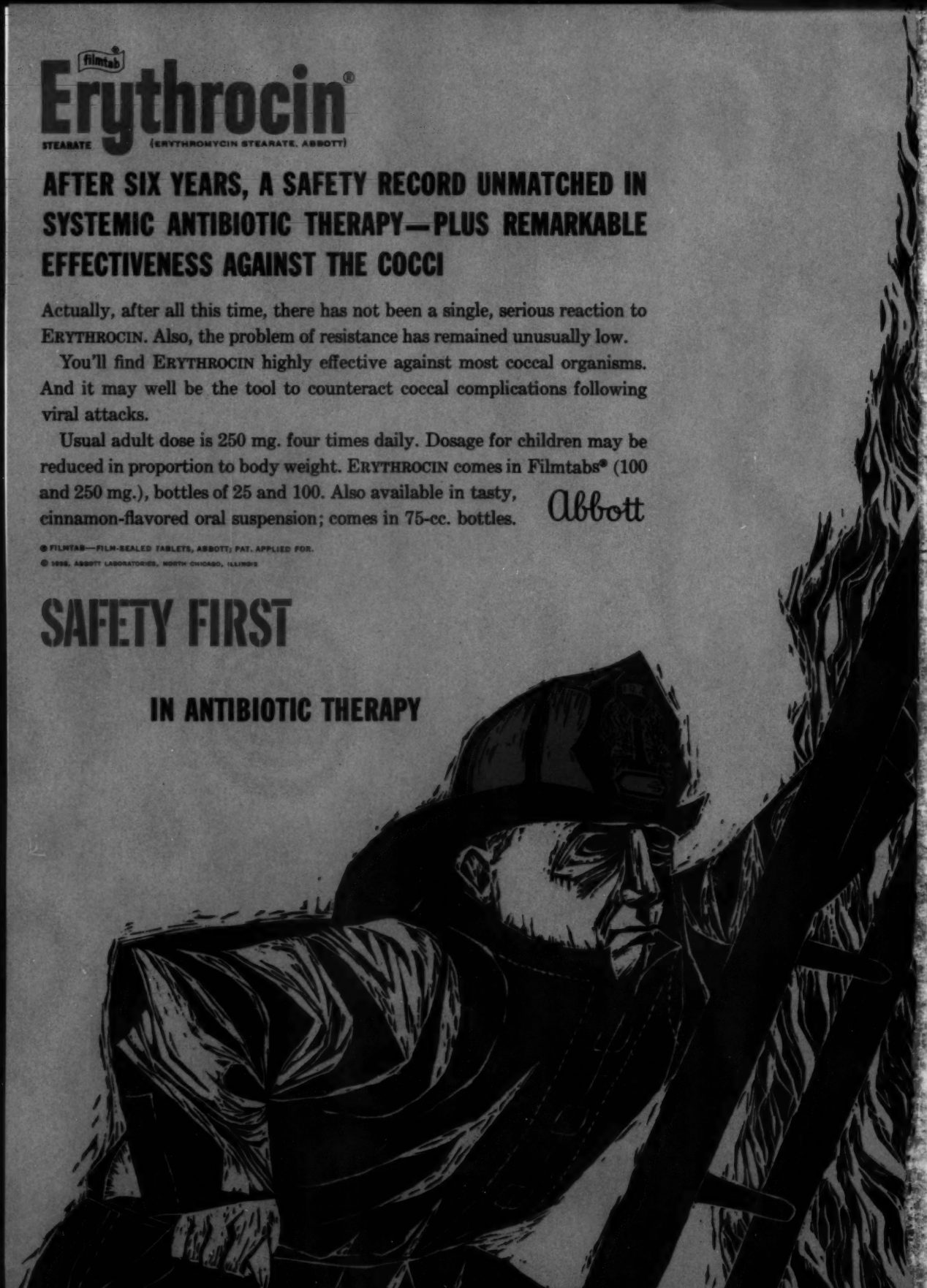

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both are often needed when
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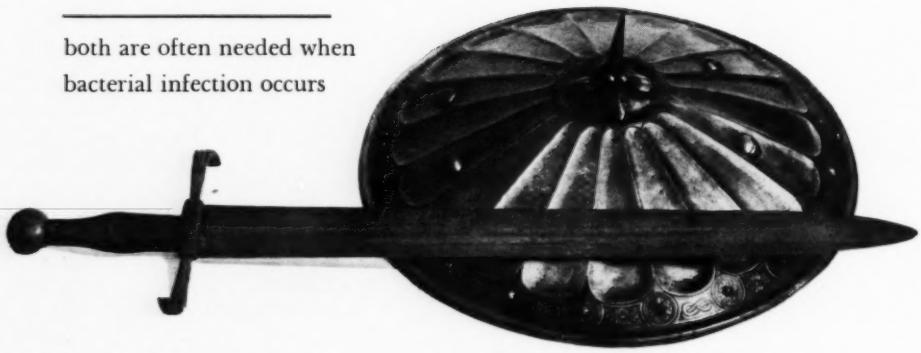

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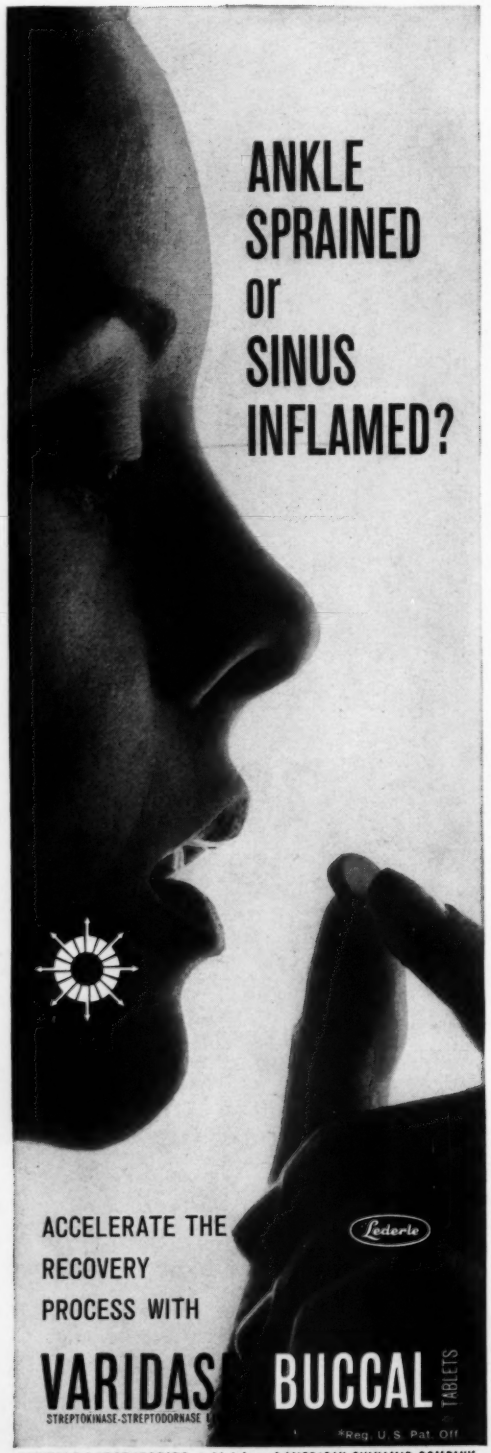

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WHOLE MILK FORMULAS

Age Months	Whole Milk Fluid Oz.	Water Oz.	Karo Syrup Tbsp.	Each Feeding Oz.	Number of Feedings in 24 Hours	Total Calories
Birth	10	10	2	3	6	320
1	12	13	3	4	6	532
2	15	13	3	4½	6	480
3	17	9	3	5	5	520
4	20	11	3½	6	5	610
5	23	11	4	6½	5	700
6	26	10	4	7	5	760
7	28	11	3	7½	5	740
8	30	11	2½	8	5	750
10	32	9	2	8	5	760
12	32	9	0	8	5	640

EVAPORATED MILK FORMULAS

Age Months	Evaporated Milk Fluid Oz.	Water Oz.	Karo Syrup Tbsp.	Each Feeding Oz.	Number of Feedings in 24 Hours	Total Calories
Birth	6	12	2	3	6	380
1	8	16	3	4	6	532
2	9	14	3	4½	5	576
3	10	15	3½	5	5	650
4	12	18	4	6	5	768
5	12	21	4	6½	5	768
6	13	22	4	7	5	812
7	14	21	3	7	5	796
8	15	20	2	7	5	780
10	16	16	1	8	4	764
12	16	16	0	8	4	704

When a feeding problem is in the making, sensible decorum will solve it. Nature invites infant feeding cooperation through hunger. If hunger is appeased on demand rather than by clock there will be fewer problems—the baby is the best judge of when he wants food and how much.

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prescribed: **Rauprote***

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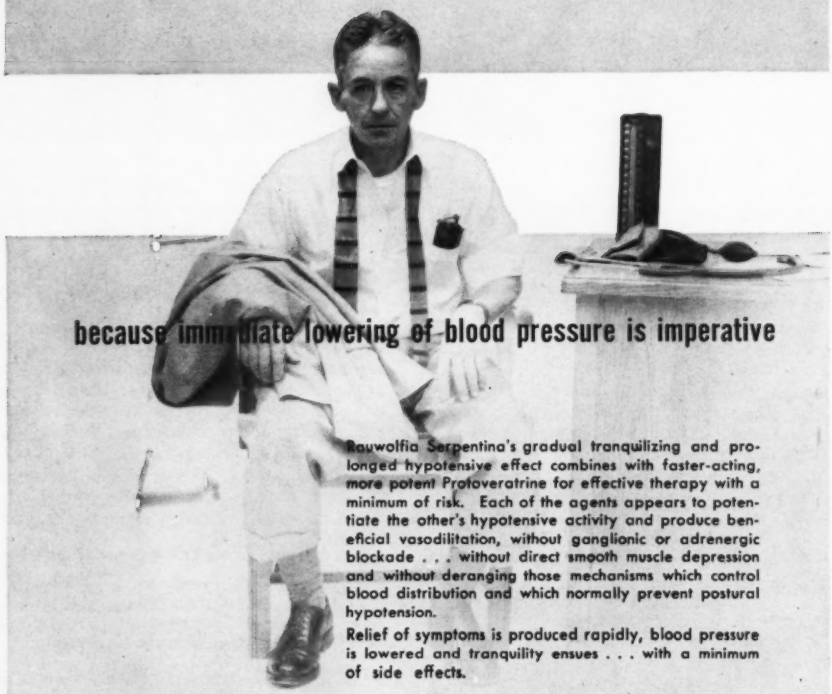

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Relief of symptoms is produced rapidly, blood pressure is lowered and tranquility ensues . . . with a minimum of side effects.

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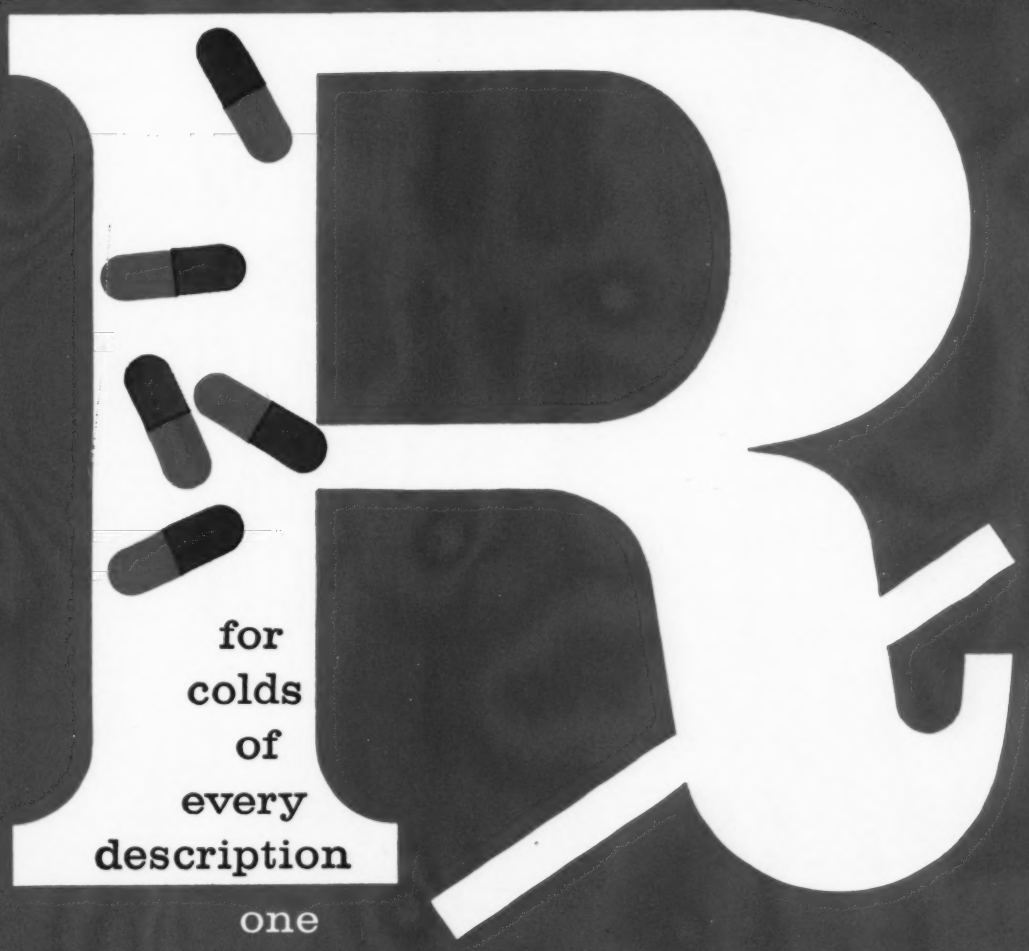

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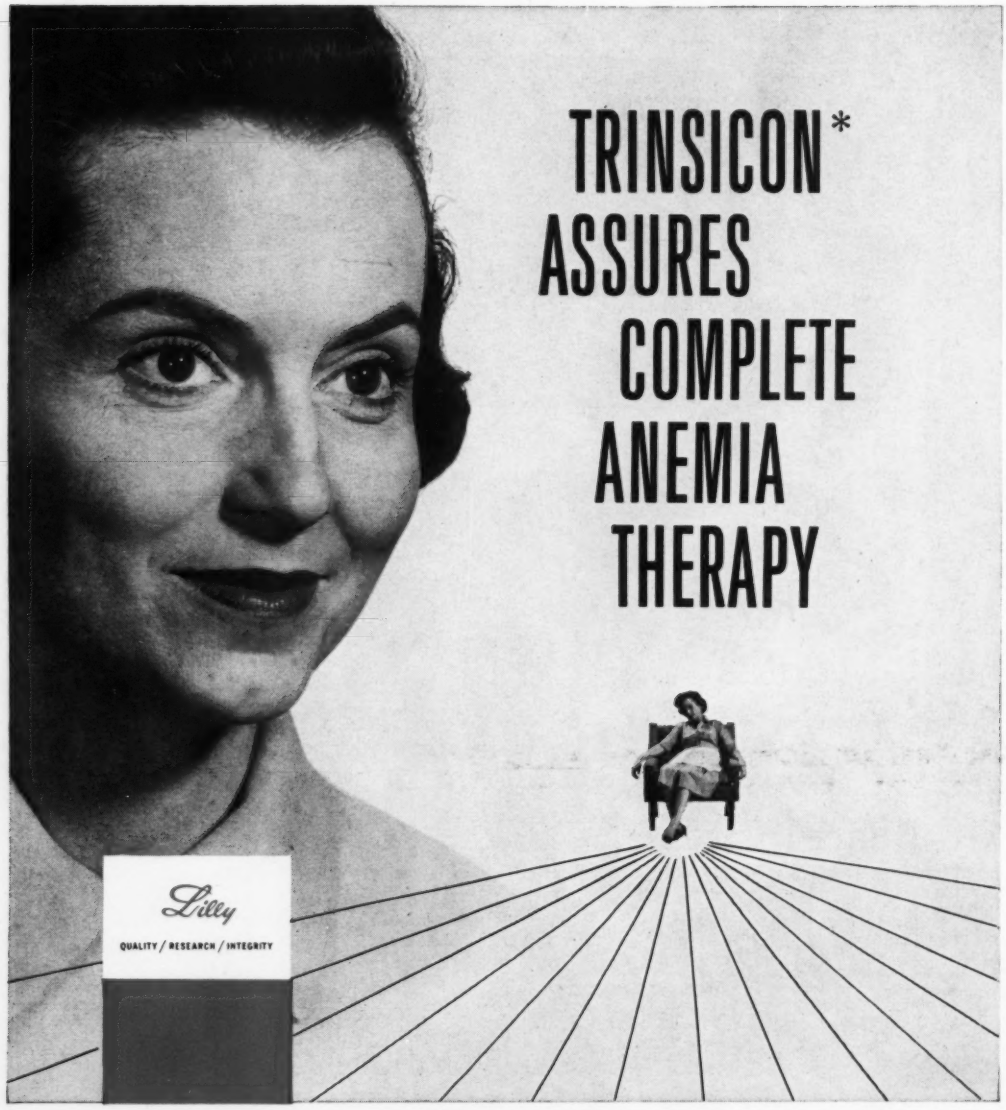

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ETIOLOGY OF ANEMIA; A PRACTICAL APPROACH TO THE SUBJECT

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The term "anemia" refers to a reduction below normal in the number of red blood cells per cubic millimeter, a reduction in hemoglobin concentration or both.

Anemia, in the language of the clinician, means a reduction of the O_2-carrying substance per unit volume of blood since this is the physiologic basis for the associated signs and symptoms, e.g., dyspnea, pallor, tachycardia, etc.

The word "anemia" is only a symptom, as is "fever" and "cough". No physician should accept a diagnosis of "anemia." However, many physicians will prescribe a "hematinic" on the finding of a low hemoglobin and look no further. Anemia, without the addition of a qualifying or descriptive term, is never a satisfactory diagnosis and never a valid basis for therapy. It must be emphasized, also, that the primary anemias are relatively rare conditions, whereas in an overwhelming majority of patients, anemia is an expression of systemic disease remote from the tissues of blood formation and destruction. Anemia should always be regarded as a danger signal demanding careful reevaluation of the patient's general condition. It is a medical blunder of the worst sort to fix one's attention upon the blood picture while a dangerous underlying disease goes unattended.

TERMINOLOGY

1. Mean corpuscular volume (or MCV or average erythrocyte volume) expresses the volume of the average red cell. It is calculated very easily from the following formula: $\text{MCV} = \frac{\text{Hematocrit x 10}}{\text{RBC in millions}}$ The normal MCV equals 87 (plus or minus 7) cu. microns. Red cells smaller than 80 cu. microns are called *microcytes*, and their occurrence as a prominent type is referred to as *microcytosis*. Red cells larger than 94 cu. microns are called *macrocytes*, and the condition of their presence is *macrocytosis*.
2. Mean corpuscular Hb. (or MCH or average Hb. content of the red blood cell) expresses the Hb content of the average red blood cell. It is calculated from the following formula: $\text{MCH} = \frac{\text{grams of Hb./100 cc. blood x 10}}{\text{RBC in millions}}$. The normal is 29 with ranges from 27 to 32 micromicrograms.

   This same information expressed in terms of the average normal is the color index (C.I.). The $\text{C.I.} = \frac{\text{Hb. (in \% of normal)}}{\text{RBC count (in \% of normal)}}$. The normal C.I. is 1.0 with a range of 0.9 to 1.1.
3. Mean corpuscular Hb. concentration (or MCHC) expresses the Hb. concentration per unit volume of red cell. It is calculated from the following formula: $\text{MCHC} = \frac{\text{grams Hb./100 cc. blood x 100}}{\text{Hematocrit in per cent}}$. The MCHC normal is 35 ($\pm$ 3) %.
4. An abnormal variation in the size of the red blood cells is referred to as *anisocytosis*.
5. Red cells of abnormal shape are called poikilocytes and their presence is spoken of as *poikilocytosis*.

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Formation of red blood cells: For the construction of red corpuscles are required amino acids, protein, iron, folic acid and vitamin B_{12}; riboflavin, nicotinic acid, pyridoxine and pantothenic acid are possibly concerned as well; certain minerals, such as copper and cobalt, are also concerned in erythropoiesis.

Under normal conditions, through increased production and transformation of yellow bone marrow to red, the bone marrow is capable of approximately a seven- or eight-fold increase in production capacity. *Destruction of red blood cells:* Wear and tear of the red blood cells result in a life span of the red corpuscles of approximately 120 days. In the average man, 9 billion red blood cells are destroyed per hour. The red blood cells are destroyed in the reticuloendothelial cells. Because there are a large number of red blood cells in the spleen, liver and bone marrow these organs are especially concerned in the process of red blood cells' destruction (and Hb. destruction). The hemoglobin liberated from the destroyed red blood cells undergoes breakdown itself. The end products of hemoglobin breakdown are iron, globin, and bilirubin.

The iron so liberated travels thenceforth as "plasma-iron" via the plasma iron-binding protein (siderophilin, a B_1-globulin) either to the bone marrow, where it is used in the synthesis of new hemoglobin, or to the storage depots where it is deposited as ferritin, a ferrous iron-protein complex, or as hemosiderin. The liberated globin is degraded and is returned to the body pool of amino acids.

Bilirubin is transported from the site of hemoglobin breakdown to the liver via the blood plasma, where it is carried with albumin as a bilirubin-albumin complex. On reaching the liver, hepatic cells separate bilirubin from albumin, then conjugate the bilirubin with glucuronic acid forming di- and monoglucurronides (di- and monoglucurronides are called together glucuronides). The glucuronides are excreted via the bile canaliculi and the bile ducts. Normally the bilirubin derived from the breakdown of hemoglobin is excreted by the liver. If the amount of bilirubin produced exceeds the excretory capacity of the liver, as in hemolytic disease, or if the outflow of bile is interrupted or diminished as a result of hepatocellular injury or biliary obstruction, bilirubin accumulates in the serum and causes jaundice.

DIRECT AND INDIRECT BILIRUBIN REACTION

One of the characteristic properties of bilirubin is its capacity to couple with the diazo reagent (van den Bergh reaction). Under some conditions the addition of the diazo reagent to bilirubin results in a prompt reaction (direct van den Bergh reaction), but under others the reaction fails to occur or proceeds only slowly unless alcohol is added to the mixture (indirect van den Bergh).

Recent studies presented evidence that the bilirubin derived from hemoglobin and discharged into the serum (where the bilirubin is attached to albumin) gives indirect reaction. On passing through the liver, the indirect-reacting bilirubin is conjugated with glucuronic acid to form the di- and monoglucuronides of bilirubin, both of which give direct van den Bergh and are excreted in the bile. Normally only a trace of the glucuronides escapes into the circulation, but under conditions of hepatocellular injury and biliary tract obstruction appreciable amounts may appear in the serum and, to a lesser extent, in the urine. The unconjugated indirect-reacting bilirubin accumulates in the serum when the rate of hemolysis is increased and also to some extent under conditions of hepatocellular injury and obstructive jaundice. The unconjugated bilirubin and the conjugated (i.e., the glucuronides of bilirubin) combine with albumin when they enter the serum, but retain their characteristic van den Bergh reactions, indicating that the linkage of bilirubin with albumin is not a factor in determining its behavior to diazo reagent. The predominant bilirubin excreted in bile and bile-containing urine are the albumin-free glucuronides of bilirubin.

Although the chemical basis for the van den Bergh reaction appears to have been clarified its physiologic significance is still

uncertain. In particular, it is not known whether the appearance of the direct-reacting glucuronides in the serum necessarily implies that bilirubin has been regurgitated from the bile ducts. Alternative possibilities that remain to be excluded are that, under pathologic conditions, the glucuronides are discharged directly into the blood or lymph from the parenchymal cells, thus permitting the conversion of indirect to direct-reacting bilirubin. The solution of this problem will do much to clarify the pathogenesis of jaundice.

Normally the urine contains no bilirubin. However, appreciable amounts may be excreted when hepatocellular or obstructive jaundice is present. In contrast, bilirubin is rare in hemolytic jaundice unless it is complicated by liver damage. All but a small amount of the bilirubin that appears in the urine is in the form of albumin-free glucuronides, from which it may be inferred that the direct-reacting bilirubin-albumin complex is more readily dissociated in the kidney than the indirect-reacting and, hence, is more readily excreted.

HEMOLYTIC JAUNDICE

Hemolytic jaundice: Characteristically, most of the bilirubin that accumulates in the serum is of the indirect-reacting type. However, there may be a slight concomitant increase in the direct-reacting fraction, although, it rarely comprises more than 10% to 15% of the total bilirubin. The absence of bile in the urine is such a striking feature that hemolytic jaundice is known also as acholuric jaundice. Due to the increase in bilirubin production, the urobilinogen in the urine and feces increase. Tests of hepatocellular function usually show no abnormalities. Occasionally, infants with erythroblastosis fetalis exhibit features suggestive of obstructive jaundice, including high levels of direct-reacting bilirubin in the serum, bilirubinuria and clay-colored stools; probably due to the presence of hepatocellular damage. Similarly, the occasional occurrence of bilirubinuria and high levels of direct-reacting serum bilirubin in adults with severe hemolytic episodes, especially following transfusion reactions, probably is attributable to complicating hepatocellular injury.

OBSTRUCTIVE JAUNDICE

Obstructive jaundice: Complete obstruction of the extrahepatic ducts leads to an increase in serum bilirubin (particularly of the direct-reacting type) the appearance of bile in the urine, the passage of clay-colored stools and the absence of urobilinogen from the urine and feces. Partial obstruction of the extrahepatic bile ducts also may give jaundice but only if the intrabiliary pressure is greatly increased, since the excretion of bilirubin does not diminish until the intraductile pressure approaches the maximum secretory pressure of 250 mm. of bile.

The functional reserve of the liver is so great that occlusion of the intrahepatic bile ducts does not give rise of jaundice unless the drainage of bile from a large segment of the parenchyma is interrupted. Thus, either of the two major hepatic ducts or a large number of secondary radicles may be occluded without producing jaundice.

Regurgitation of bilirubin is thought to be the principal factor involved in the pathogenesis of obstructive jaundice. It is postulated that, as a result of increased intraductile hydrostatic pressure, the walls of the canaliculi and the terminal bile ducts rupture or become more permeable, permitting the escape of direct-reacting bilirubin in the blood. The increase in the indirect-reacting fraction that almost invariably is present in obstructive jaundice is thought to be due to a decrease in the excretory capacity of the liver (resulting in the retention of indirect-reacting bilirubin).

HEPATOCELLULAR JAUNDICE

Hepatocellular jaundice: Due to a reduction of the excretory capacity of the liver, the indirect-reacting bilirubin cannot be excreted properly, hence, elevation of the indirect-reacting bilirubin (as in hemolytic disease). Usually, however, the serum also contains an excess of direct-reacting bilirubin; bilirubin is excreted in the urine and fecal urobilinogen is reduced. Urine urobil-

inogen may be increased, since the parenchyma no longer is cabable of clearing the serum of urobilinogen entering from the intestinal tract. However, the excretion of bilirubin may be suppressed to such an extent that virtually no bilirubin reaches the intestine. Under these conditions the stools are clay-colored, production and reabsorption of urobilinogen in the intestine are diminished and the excretion of urobilinogen in urine falls to a low level. Thus, hepatocellular jaundice can seldom be differentiated from obstructive jaundice solely on the basis of changes in bilirubin metabolism.

Retention of bilirubin is an important factor in the pathogenesis of hepatocellular jaundice, particularly since the serum invariably contains an excess of indirect-reacting bilirubin. However, the concomitant accumulation of direct-reacting bilirubin in the serum suggests that regurgitation also plays a role.

Although the changes in bilirubin metabolism appear to be identical in hepatocellular and obstructive jaundice, certain other biochemical abnormalities serve to differentiate them. Thus, in hepatocellular jaundice the thymol turbidity and cephalin-cholesterol flocculation are increased, while in obstructive jaundice, the serum levels of alkaline phosphatase and cholesterol tend to rise sharply.

Hemoglobinuria, methemoglobinuria, and methemalbuminuria: Under pathologic conditions free hemoglobin may escape into the circulation. This occurs in severe hemolytic states when there is intravascular hemolysis, as in erythroblastosis fetalis, blackwater fever and Clostridia sepsis. Such hemoglobin is promptly bound by an -globulin and is carried to the reticuloendothelial system for breakdown there and conversion to bilirubin. Free hemoglobin is demonstrable in plasma only when the hemoglobin-binding capacity of the plasma is exceeded. In such instances the hemoglobin is converted to methemoglobin or to methemalbumin. It is the free, unbound hemoglobin which appears in the urine. Thus, hemoglobinuria, methemoglobinuria and methemalbuminuria develop.

CAUSES OF ANEMIA

Since normally, the number of red blood cells in the blood remains within narrow limits, it follows that the rate of cell destruction is equal to that of formation. It is evident, therefore, that anemia results either from an increase in the rate at which the cells are destroyed or lost, or from a decrease in the rate at which they are formed. On this basis, the anemias may be classified as:

I. Anemias due to increased rate of cell loss
II. Anemias due to increased rate of cell destruction, and
III. Anemias due to decreased rate of cell formation.

TABLE I.

CAUSES OF ANEMIA (ETIOLOGIC CLASSIFICATION OF ANEMIA)

I. *Anemias due to increased loss of red blood cells*
   a. Acute loss of blood
   b. Chronic loss of blood
II. *Anemias due to increased destruction of red blood cells* (also called "Hemolytic anemias"
   A. *Extracorpuscular causes*
      1. Chemical agents and drugs:
         a. Related to size of dose: benzene, acetanilid, lead, naphthalene, aniline, phenacetin, arsine, etc.
         b. Depending on hypersensitivity of the patient's red blood cells: sulfonamides, quinine, pamaquine, primaquine, benzedrine, etc.
      2. Infectious agents:
         a. Septicemia
         b. Parasites: malaria (Oroya fever)
      3. Animal and vegetable poisons: snake venoms, fava bean, castor oil bean, mushrooms
      4. Burns
      5. Liver disease
      6. Uremia
      7. Hypersplenism
      8. Anemias due to immune body reaction:

a. Virus infections: rubella, varicella, infectious mononucleosis, atypical pneumonia
b. Isoagglutinins anti-A, anti-B (transfusion reaction)
c. Isoagglutinins anti-Rh, anti-Hr, Kell, Duffy, etc. (erythroblastosis fetalis, intragroup transfusion reactions)
d. Paroxysmal cold hemoglobinuria (cold hemolysins)
e. Chronic infections, especially granulomatous infections, as tuberculosis, brucellosis, sarcoidosis, histoplasmosis, malaria
f. Congestive splenomegaly, due to any condition producing elevation of pressure in the portal vein system
g. Infiltrative splenomegaly, especially diseases like Gaucher's disease
h. Collagen diseases, including polyarteritis nodosa, systemic lupus erythematosus, scleroderma and rheumatic arthritis
i. Myelofibrosis, chronic leukemia, Hodgkin's disease, and lymphosarcoma
j. Splenic neoplasms and cysts

B. *Intracorpuscular defects*
1. Hereditary spherocytosis (also called congenital hemolytic anemia or congenital hemolytic jaundice or chronic familial icterus, etc.)
2. Hereditary nonspherocytic hemolytic anemia
3. Hereditary leptocytosis (also called thalassemia, Cooley's anemia, target-cell anemia, Mediterranean anemia)
4. Sickle-cell anemia
5. Other hereditary hemoglobinopathics (C, D, E, G, H, I, J, K)
6. Paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli syndrome)
7. Acquired hemolytic anemia

III. *Anemias due to decreased rate of cell formation.* These anemias may be caused by inhibition of the rate of cell formation by the bone marrow or by replacement of the bone marrow by other tissues.

A. Inhibition (depression) of the rate of red blood cell formation (inhibition of bone marrow activity):
1. Chronic infections (anemia associated with chronic infections)
2. Chronic diseases
3. Chemical agents
4. Physical agents (physical injury of bone marrow): x-ray, radium, atomic explosion, other radioactivity
5. Uremia
6. Diffuse carcinomatosis

B. Mechanical interference with blood formation in the bone marrow (Mechanical displacement of the bone marrow; mechanical replacement of the bone marrow). Also called myelophthisic anemia
1. Leukemia
2. Hodgkin's disease
3. Myelofibrosis
4. Malignancy with metastases to the bone marrow
5. Multiple myeloma
6. Marble bone disease and various other congenital bone diseases are less common causes.

C. Decreased formation of red blood cells due to deficiency of substances necessary for their production
1. Deficiency of vitamin B_{12}
2. Deficiency of folic acid
3. Deficiency of iron
4. Deficiency of protein
5. Possible deficiency of vitamin C may cause anemia
6. Endocrine deficiency; myxedema, adrenal insufficiency and pituitary insufficiency
7. Liver disease

I. Anemias due to increased loss of red blood cells: The simplest mechanism by which anemia develops is blood loss. Anemia due to blood loss may be caused by acute (sudden, rapid) blood loss or chronic (insidious) blood loss.

a. Anemia due to acute loss of blood (given by some authors under the name "acute posthemorrhagic" anemia) is caused by rapid loss of a large amount of blood. Massive hemorrhage may be due to trauma, peptic ulcer, spontaneous rupture of aneurysms, esophageal varices, hemorrhagic diathesis, etc.

b. Chronic blood loss anemia differs from acute blood loss anemia in that it results from a slow depletion of blood beyond the replacement capacity of the bone marrow. Chronic loss of blood occurs most commonly from the pelvic organs in female and from the gastrointestinal tract in the male.

II. Anemias due to increased destruction of red blood cells (Hemolytic anemias): The term hemolytic anemias refers to anemias in which there is an increased rate of destruction in red blood cells. The bone marrow is able to increase its production seven to eight times; however, if the destruction is more than this, anemia will appear because the bone marrow is unable to compensate for any more destruction. This destruction of red blood cells may be due to extracorpuscular causes (extracorpuscular causes act to cause destruction of normally formed cells) or intracorpuscular defects (defective formation of the red blood cells leads to their early destruction). These intracorpuscular defects usually are hereditary, and often congenital.

Mechanism of hemolysis: Various processes condition or cause the destruction of red blood cells: phagocytosis, agglutinins and hemolysins, osmotic lysis, mechanical factors and sequestration with erythrostasis.

A. Extracorpuscular causes:

1. Various chemical agents and drugs can destroy the red blood cells, thus causing hemolytic anemia. Some of them cause anemia because they destroy the red blood cells (or only when in large doses), others cause anemia because of hypersensitivity of the red blood cells to them.
2. Infectious agents:
   a. Septicemia, especially due to Clostridium Welchii, cholera, and less frequently streptococci, staphylococci, meningococci, can cause destruction of red blood cells.
   b. Parasites: malaria and artonella can destroy red blood cells. Malaria, as seen further below, can destroy red blood cells not only because of its presence in the red blood cell (mechanical effect) but also because of formation of immune bodies which cause hemolysis of the red blood cells.
3. Animal and vegetable poisons can cause hemolysis.
4. Burns can cause hemolysis.
5. Liver diseases can be accompanied by hemolysis of red blood cells.
6. Uremia can cause increased destruction of red blood cells.
7. Hypersplenism: The anemia accompanying certain disorders involving the spleen has been attributed to an exaggeration of the normal functional activities of the organ ("hypersplenism"), which include the removal of worn-out red blood cells.
8. Anemias due to immune body reaction: the classical representatives of these anemias are the erythroblastosis fetalis and transfusion reaction.
   a. Virus infections: Rubella, varicella, infectious mononucleosis and atypical pneumonia may cause hemolysis of red blood cells due to formation of autoimmune bodies.
   b. Isoagglutinins anti-A and anti-B: The processes that take place in transfusion reaction are well known.
   c. Isoagglutinins anti-Rh, an-

ti-Hr, Kell, Duffy, etc.: The processes that take place in erythroblastosis fetalis are well known.

d. Paroxysmal cold hemoglobinuria: This rare disease is due to sudden intravascular hemolysis caused by the action of an autohemolysin contained in the patient's serum. This hemolysis has the peculiar property of being activated at low temperatures, but exhibits its destructive action on the red cells only after the blood is warmed again.

e. Chronic infections may cause the formation of autoimmune body reaction causing hemolysis of the red blood cells. This is isoimmunization.

f. Congestive splenomegaly may cause isoimmunization (autoimmunization).

g. Infiltrative splenomegaly may cause hemolysis of red blood cells due to formation of immune bodies.

h. Collagen diseases may cause hemolytic anemia because of formation of immune bodies.

i. Myelofibrosis, chronic leukemia, Hodgkin's disease, lymphosarcoma, can cause anemia by mechanical replacement of the bone marrow, but can also cause the formation of immune bodies to which the red blood cells are sensitive and so undergo hemolysis.

j. Splenic neoplasms and cysts may be the cause for formation of autoimmune bodies which cause destruction of red blood cells.

9. Acquired hemolytic anemia: The term "acquired hemolytic anemia" is used for a rather broad group of non-hereditary hemolytic anemias.

B. Intracorpuscular defects:

1. Hereditary spherocytosis: The disease is due to an inherited defect (transmitted as a Mendelian dominant by either parent) of the red blood cells, which tend to be more spheroid than normal and thus are more subject to destruction. (The spleen is the principal site for destruction of abnormal red blood cells.)

2. Hereditary nonspherocytic hemolytic anemia: This disorder resembles hereditary spherocytic anemia in the mode of inheritance; however, it differs in that the anemia is generally macrocytic, spherocytes are not found and osmotic fragility is normal.

3. Hereditary leptocytosis (Mediterranean anemia, Thalassemia) is an inherited disorder. The disorder is due to the inheritance of a factor which leads to defective hemoglobin synthesis, namely, the red blood cells in this disease contain a variable and often large proportion of fetal hemoglobin.

4. Sickle-cell trait and sickle-cell anemia are due to an inherited abnormality of the hemoglobin, namely, the red blood cells in sickle-cell trait and sickle-cell anemia contain an abnormal hemoglobin, termed hemoglobin S. The red blood cells show increased mechanical fragility and break up easily.

5. Other hereditary hemoglobinopathies (C, D, E, G, H, I, J, K): Now it is known that beside the normal hemoglobin found in normal red blood cells, sometimes, the bone marrow produces abnormal hemoglobin. There are several types of abnormal hemoglobins. The normal hemoglobin is termed hemoglobin A. The abnormal hemoglobins so far identified are: hemoglobin

S (this is the hemoglobin found in sickle-cell trait and sickle cell anemia), hemoglobin-C, hemoglobin-D, hemoglobin-E, hemoglobin-G, hemoglobin-H, hemoglobin-I, and hemoglobin-K. All the anemias due to abnormal hemoglobin are now called hemoglobinopathies and sickle-cell anemia is their prototype.

6. Paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli syndrome): The fault in this disorder resides in the red blood cells, which are unusually susceptible to acid hemolysis.

III. Anemias due to decreased rate of cell formation:

A. Inhibition (depression) of the rate of red blood cell formation can be caused by:

1. Chronic infections, such as tuberculosis (it was mentioned above that tuberculosis can cause anemia also by autoimmunization of red blood cells), chronic sepsis, osteomyelitis, salpingitis, sinusitis, subacute bacterial endocarditis, etc.: How the chronic infections cause anemia is not known; however, it has been observed that infection causes a profound disturbance of iron metabolism with decreased incorporation of iron into hemoglobin. So it seems likely that some fault in the construction of red blood cells is an important underlying mechanism.
2. Chronic diseases: Various chronic diseases, such as chronic nephritis and rheumatoid arthritis can cause anemia by depressing the bone marrow. The pathogenesis of anemia associated with chronic renal disease is an enigma; in certain instances there is increased hematolysis, in others, there is decreased blood formation. Unlike the anemia associated with infection, anemia of renal insufficiency does not have hypoferremia as a constant feature.
3. Certain chemical agents depress the formation of red blood cells by the bone marrow. Individual sensitivity and some obscure mechanism leading to bone marrow aplasia seem to be involved in the anemia which follows ingestion of certain drugs and chemicals.
4. Physical agents: The anemia which follows exposure to irradiation is probably related to the inhibition of nucleic acid synthesis. Here too, however, there is some evidence that hemolysis also is a factor.
5. Uremia.
6. Diffuse carcinomatosis may cause anemia due to toxic metabolic state.

B. Mechanical interference with blood formation in the bone marrow (Mechanical displacement of the bone marrow; mechanical replacement of the bone marrow): This type of anemia is called myelophthisic anemia. The replacement of the bone marrow can be caused by leukemia, Hodgkin's disease, myelofibrosis, malignancy with metastases to the bone marrow, multiple myeloma; marble bone disease and various other congenital bone diseases are less common causes. However, now there is evidence that the anemia is due not only to the bone marrow replacement but also to the fact that the "life span" of the red blood cells is reduced and occasionally frank hemolytic anemia develops.

C. Decreased formation of red blood cells due to deficiency of substances necessary for their production: Deficiency of the following substances may cause anemia: vitamin B_{12}, folic acid, iron, protein. Anemia also may be present in myxedema, anterior pituitary insufficiency and adrenal cortex insufficiency. The

pathogenesis of the anemia observed in myxedema is obscure; this anemia disappears gradually as desiccated thyroid is given. The pathogenesis of anemia with adrenal and pituitary insufficiency is not understood. Anemia may be present in liver diseases.

CLINICAL FEATURES OF ANEMIA

Clinical features of anemia: Hemoglobin is the vehicle for supply of oxygen to the tissues. Approximately one half of the O_2-carrying substance (hemoglobin) can be lost before recognizable signs and symptoms appear. Nevertheless, it must be remembered that the effects of anemia are felt in every organ and tissue. The development of symptoms in association with anemia depends on: (1) the rapidity with which anemia has developed, (2) the degree of reduction in the O_2-carrying power of the blood, as well as the extent of changes in total blood volume and (3) the causative disorder.

If anemia has developed so rapidly that there has been little or no time for physiologic adjustment, the symptoms are likely to be prominent and to appear comparatively early. On the other hand, if the anemia has been insiduous in onset, the tissues of the body adjust themselves to the gradually diminishing supply of O_2 so that the red cell count may be as low as two million cells per cubic millimeter, or the hemoglobin as low as 6 gm. per ml. may develop without the appearance of any symptoms. Reaction to a sudden loss of blood is referable more to reduced blood volume than to the actual removal of red blood cells and hemoglobin. Or, in other words, when anemia is caused by sudden loss of blood, the most prominent symptoms are those resulting from the reduction of total blood volume, and they are relieved in large measure when the loss of blood is replaced, by absorption of fluid from the tissues or by the artificial introduction of fluid or red blood cells. The chief symptoms arising with rapid destruction of blood are those associated with the disposal of the products of blood destruction (hemolysis), namely, hemoglobinuria and jaundice.

Patients with anemia present many nonspecific clinical signs and symptoms. They are pale, complain of weakness, malaise, easy fatigibility, headache, dyspnea on exertion, vertigo, palpitation, faintness, increased sensitivity to cold, tinnitus or roaring in the ears, black spots before the eyes, muscular weakness, easy irritability. Drowsiness develops in severe anemia. Loss of appetite is not uncommon. Nausea, flatulence, abdominal discomfort, vomiting or abnormal appetite may also be found. In pernicious anemia, and less often, in chronic hypochromic anemia, glossitis and atrophy of the tongue and papillae are common. Necrotic lesions in the mouth and pharynx may develop in patients with aplastic anemia, in granulocytopenia and in acute leukemia. Menstrual disturbances, most often amenorrhea, in the female, and loss of libido in the male are frequently encountered in severe anemia. In other instances, excessive menstrual bleeding accompanies anemia. Slight proteinuria may be present. If the quantity of superficial fat is the criterion, the nutritional state may appear to be moderately or well preserved, in spite of the presence of anemia. Fever of mild degree is common when the anemia is severe. Anemia is one of the most common causes of palpitation, shortness of breath and pallor.

Paresthesias are common in pernicious anemia and they may be accompanied by signs and symptoms of extensive peripheral nerve and spinal cord degeneration. They also may be encountered in chronic hypochromic anemia, but in the latter, spinal cord degeneration is very rare. The arterial pulsation and the pulse pressure are increased. The heart may be dilated (due to increased venous return to the heart.) The circulation time is shortened. When this increase in inflow load exceeds the reserve power of the myocardium, the clinical picture of cardiac failure ensues. Edema is a frequent accompaniment of anemia. The cause of edema are hypoproteinemia and diminished tissue 0_2 tension leading to increased capillary permeability. Severe anemia may produce a systolic murmur, which usually is most marked at the pulmonic area but may be heard elsewhere over the

precordium. Over the vessels of the neck, a curious humming sound, the bruit de diable, may be heard. Enlargement of the spleen is frequent in anemias of long-standing. When there is iron deficiency the nails lose their luster, become brittle, break easily and may become concave instead of convex (koilonychia).

Cyanosis is not common in severe anemia because there is insufficient circulatory hemoglobin to produce the dusky blue discoloration of reduced hemoglobin. Anemia may cause fatty degenerative changes in the myocardium and if these changes are severe cardiac failure may develop. Occasionally, the myocardial anoxia (due to diminished oxygen-carrying substance (hemoglobin) manifests itself by pain on exertion (angina pectoris), particularly when pre-existing vascular disease has already rendered the myocardium partially ischemic.

In addition to the above general signs and symptoms, there are many clinical findings characteristic of the etiologic type of anemia. The most characteristic features of the anemias become evident only with laboratory studies of the peripheral blood.

Detection of anemia: The presence or absence of anemia is determined by the examination of the blood, but its existence may, nevertheless, be suspected with fair accuracy on the basis of the above symptoms and signs. The skin itself is an unreliable index of anemia; the mucous membranes, the nailbeds and the palms of the hands are more dependable. The color of the conjunctiva may be very helpful. The gums are not so useful as would be expected. Unless the hand has been held in an awkward position or has been exposed to cold or excessive heat, the nailbeds and the palms of the hands will reveal anemia if it is marked.

STUDY OF A PATIENT WITH ANEMIA

A. The history must give attention to the following details:
   1. The possible occurrence of blood loss
   2. The diet, particularly with reference to the intake of foods rich in protein, vitamins and minerals
   3. The presence or absence of symptoms suggesting an underlying disease, as chronic renal disease, chronic infection or malignancy
   4. In the case of a child or adolescent, the rate of growth
   5. In the case of a woman, the nature of the menstrual periods (amount of flow, duration and frequency)
   6. The possibility of exposure to poisons that may cause anemia
   7. The family history: A history of splenectomy in some member of the family may be a valuable clue to the diagnosis. If a familial or hereditary disorder is suspected other members of the family should be examined if possible, since the family may be unaware of the existence of any detectable abnormality.

B. The physical examination should be complete and the examiner alert to look for the signs of anemia as given above under "Clinical features of anemia."

C. The laboratory examination: The following procedures are used in investigation of anemias:
   1. If anemia is suspected start the investigation with ordering hematocrit. If the hematocrit is reduced, order hemoglobin and red blood cell count.

      (Note: The presence or absence of anemia can be determined from the red blood cell chamber count, the hemoglobin, or the hematocrit. The hematocrit is much more accurate, the next in accuracy is hemoglobin and the least accurate is the red blood cell count.)
   2. From the hematocrit, hemoglobin and the red blood cell chamber counting, ask the laboratory to calculate (or calculate yourself from the formulae given under "Terminology") the

MCV, the MCH, the MCHC and C.I. These findings should be checked by examination of smear.

3. Ask for a blood smear made directly from the finger. Blood smear should be examined in all instances of suspected anemia because it yields valuable information. Namely ask the laboratory for the following: (a) Morphologic description of the red blood cells in stained smear. (The morphology of the cells may serve as a valuable clue to the nature of the anemia.) (b) In the smear may be found evidence of exaggerated erythropoiesis, such as polychromatophilic red cells, macrocytes and even nucleated red cells. (c) Evidence of disturbed red cell formation, such as poikilocytes, Cabot rings and Howell-Jolly bodies may also be found. (d) The smear may reveal an unsuspected protozoal parasite (e.g., that of malaria).
4. WBC, platelet count and differential count: The hematopoietic system functions as a physiologic unit, consequently, when red cell formation is stimulated it is found as a rule there is, in addition, increased leukopoiesis and an increase in the quantity of platelets. Thus, following acute blood loss, there may be not only reticulocytosis but also moderate or even marked leukocytosis accompanied by an increase in the younger forms of leukocytes ("shift to the left").
5. Reticulocyte count
6. Evidences of increased red cell destruction must also be sought out. The clue to this is the plasma bilirubin level. The van den Bergh reaction reveals this to be of the "indirect" type, and examination of the urine in such cases reveals an increased quantity of urobilinogen. It is useful to measure the quantity of urobilinogen excreted in the stool as well. So order icterus index, plasma bilirubin, van den Bergh, urine urobilinogen and stool urobilinogen.
7. Coagulation time
8. Bleeding time
9. Clot reaction time
10. Capillary resistance (Rumpel-Leede sign, tourniquet test)
11. Ask for variation in size (anisocytosis), shape (poikilocytosis), hemoglobin content and staying quality of red blood cells.
12. If there is reason (as for example, elevated plasma bilirubin) to believe that one is dealing with a hemolytic anemia, ask for the following special procedure which will aid in the differential diagnosis: (a) Osmotic fragility of the red blood cells. (b) Coombs' test. (c) Test for warm, cold and acid hemolysins. (d) Investigate the presence of abnormal hemoglobin (by lab. tests). (e) Mechanical fragility.
13. If the cause of the anemia is not found from the history, plasma iron concentration should be ordered. The plasma concentration is reduced below the normal in cases of iron deficiency, in association with the anemia of chronic infection and in various types of anemia in which blood regeneration is active.
14. When the patient has been studied thoroughly in the manner indicated above, the number of instances in which examination of the bone marrow will be required is small.
15. In the study of bone marrow (as obtained by sternal, iliac crest, spinous process or rib puncture) ask the laboratory for the following: (a) Is M:E ratio (myeloid:erythroid) increased? (b) Is there normoblastic hyperplasia?

(c) Is there an increase of non-myeloid cells? (d) Is there megaloblastic hyperplasia?

INTERPRETATION OF RESULTS

After obtaining an answer to questions (a), (b), (c), and (d) consult the table below: (a) M:E ratio is increased in: myeloid forms of leukemia, the majority of infections, leukemoid reaction, decrease in nucleated red cells. (b) Normoblastic hyperplasia is present in: hemorrhagic anemias, iron-deficiency anemia, hemolytic anemia, thalassemia, cirrhosis of the liver, polycythemia vera, plumbism, anemia of chronic renal disease. (c) Non-myeloid cells are increased in: other forms of leukemia, multiple myeloma, metastases from carcinoma to the bone marrow, Gaucher's disease, Niemann-Pick disease, aplastic anemia (relative increase only), infectious mononucleosis. (d) Megaloblastic hyperplasia is present in: pernicious anemia, sprue, idiopathic steatorrhea, resection of small intestine (certain cases), tropical macrocytic anemia, nontropical nutritional macrocytic anemia, macrocytic anemia with diphyllobothrium infestation, megaloblastic anemia of infancy, megaloblastic anemia of pregnancy.

Although in all cases of anemia the examination of bone marrow is of interest, bone marrow examination is an essential aid in diagnosis only in a limited number of conditions. These include aleukemic leukemia, multiple myeloma, Gaucher's disease, Niemann-Pick disease, and unusual cases of macrocytic anemia. In "aleukemic" leukemia, the bone marrow reveals numerous immature forms, thus dispelling the doubt raised by their absence or scarcity in the blood. In addition to these disorders, it may be added that, in cases of parasitic diseases such as kala-azar, the causative organisms may be discovered in the bone marrow, when they cannot be found in any other way. Again, the cells of metastatic lesions may be demonstrated by bone marrow examination. In aplastic anemia, it is the negative character of the marrow material which may be helpful.

I. Anemia due to excessive blood loss: The anemia caused by blood loss may be due to sudden loss of large amount of blood or chronic loss of blood. It is convenient to consider acute and chronic posthemorrhagic anemias separately because their manifestations and, in certain respects, their treatment differ so greatly. It should be realized, however, that these two syndromes represent two extremes and that, in practice, variations will be encountered which represent all stages between these extremes.

A. Anemia due to acute loss of blood (also called "acute posthemorrhagic anemia"): The immediate effects of hemorrhage depend upon the rapidity and amount of blood loss. Sudden loss of ⅓ of the blood volume may prove fatal but as much as ⅔ may be lost over a 24-hour period without fatal outcome. The rapid loss of blood leads to reduction of blood volume and the clinical manifestations are due mainly to low blood volume. If the blood loss is great "acute posthemorrhagic shock" develops. Generally speaking, symptoms are likely to appear sooner and are more pronounced in relation to the amount of blood lost when the bleeding is external than when it is not recognized by the patient. The symptoms of acute blood loss are pallor, faintness, restlessness, palpitation, sweating, weak, rapid pulse, rapid shallow respiration, dizziness, thirst and falling blood pressure. If the patient survives the hemorrhage, the build-up of the plasma volume leads to hemodilution that reaches full extent within 72 hours.

Laboratory findings:

1. Red blood cell count, hemoglobin, and hematocrit: Examination of the peripheral blood during and immediately after hemorrhage shows no numerical or morphological changes in the cells since red blood cells and plasma are lost at the same time: the red blood cell count, hemoglobin and hematocrit are

deceptively high. Within a few hours, fluid enters the circulation from the tissues resulting in hemodilution and a drop in the red cell count and the hemoglobin proportional to the severity of the bleeding. The resulting anemia is normocytic and normochromic, however, several days later, when the bone marrow commences to produce rapidly a large number of red blood cells to replace the lost, immature red corpuscles are liberated from the bone marrow, and because these immature red corpuscles are larger than the normal mature red cells, the anemia may become macrocytic normochromic.

2. Leukocytosis: Polymorphonuclear leukocytosis as high as 35,000 may take place within the first few hours after severe hemorrhage, with "shift to the left." Polymorphonuclear leukocytosis with shift to the left is the first discernible blood change following acute hemorrhage.
3. An increase in the number of platelets often takes place.
4. Reticulocytosis appears several days after the hemorrhage. Reticulocytes may begin to appear within 48 hours following a brisk hemorrhage and may continue to increase for several days. A persistent reticulocytosis forming a plateau-like curve, suggests that bleeding is continuing for cessation of hemorrhage is marked by quick regression of the signs of stimulated hematopoiesis. (Note: Because the bone marrow acts as a hemopoietic unit, when stimulated to produce red blood cells, the bone marrow also produces WBC and platelets.) So the signs of stimulated hematopoiesis are: (a) Rising blood cells; (b) Appearance of immature red blood cells; (c) Leukocytosis; (d) Shift to the left; (e) Reticulocytosis; (f) Appearance of immature granulocytes; (g) Polychromatophilic cells appear several days after the acute hemorrhage. (h) As we have stated, the anemia in acute hemorrhage is normocytic normochromic and several days after the hemorrhage, it may become macrocytic normochromic. If the iron stores of the body are good and the blood loss has not been extreme, there is no hypochromic, or it is slight. But when the drain on the iron is greater than can be readily replenished, the anemia may become hypochromic. (i) When the acute hemorrhage is internal, destruction of the blood and absorption of the products may lead to an increased excretion of urobilinogen in the urine and stools and, rarely, even slight bilirubinemia may be found. (j) Bowel hemorrhage is often associated with an increase in the blood urea nitrogen level and low grade fever 48 hours later.

Following loss of blood from the body, regeneration of blood occurs, and in an otherwise normal individual, the blood values are brought to normal within a short period of time depending upon the amount of blood lost.

B. Chronic blood loss anemia differs from the acute blood loss anemia in that it results from a slow depletion of blood beyond the replacement capacity of the bone marrow. In this condition, the critical factor is iron depletion. The chronic blood loss drains the iron reserves and with this deficiency the marrow cannot form red cells. The anemia is, therefore, strictly an iron deficiency anemia. Chronic blood loss anemia is seen commonly in such conditions as gastric or duodenal ulcer, bleeding hemorrhoids, ulcer-

ating neoplasm and, less commonly, in certain blood disorders in which hemorrhages occur.

When blood is lost in small amounts over a long period of time it appears that the bone marrow is not stimulated to replace the cells as it would be if the blood loss was more acute or of larger quantity. So the peripheral blood pattern of chronic blood loss combines the features of iron deficiency anemia with the signs of bone marrow suppression, or at least subnormal hematopoietic function. When massive hemorrhage complicates the course of chronic blood loss the picture becomes one of iron deficiency plus active red cell formation. The laboratory pattern described below is the more common one of iron deficiency without release of new red blood cells into the blood:

1. Anemia: In the majority of cases, the red cell count is only moderately diminished. The erythrocystic morphology is microcytic and hypochromic; the volume index and color index are below 0.9.
2. Altered red cell morphology: In the stained film, the red cells are small and poorly filled with hemoglobin. Irregular, pear-shaped, or tailed poikilocytes are common. Polychromatophilic cells and nucleated forms are not seen in the smear.
3. Leukopenia: As a rule, there is low WBC count, and there is a relative lymphocytosis.
4. Low reticulocyte count, unless there has been a recent acute bleeding episode.
5. The icterus index and the bilirubin are low.

II. Anemia due to increased destruction of red blood cells, also called "hemolytic anemias." Diagnosis:

1. The symptoms depned upon the rapidity, extent of hemolysis and its duration.
2. Symptoms may be entirely absent or there may be few manifestations.
3. The patient may complain from symptoms of anemia in general (see above "Clinical features of anemia").
4. The patient may presently, or may have had in the past, symptoms of hemolytic crisis. This is characterized by the following: a severe, shaking chill, followed by high fever, malaise, headache and pain in the back, abdomen or limbs; the urine becomes very dark, jaundice develops rapidly; as anemia ensues, weakness, palpitation, dyspnea, tachycardia, hemic murmurs, faintness and other manifestations of anemia appear.
5. In chronic hemolytic anemia, splenomegaly is common and enlargement of the liver may be present.
6. All grades, from acute fulminating disorders of several days' duration to extremely benign conditions of many years' standing, may be encountered.
7. A chronic process may be interrupted by acute exacerbations.
8. Laboratory findings:
   a. Red blood cell count, hemoglobin and hematocrit: The anemia may be mild or severe, depending upon the intensity and duration of the hemolytic process.
   b. The anemia is usually normocytic, but may be macrocytic.
   c. Following a hemolytic crisis, there will be rapid regeneration of red blood cells; look for signs of increased red cell production: reticulocytosis, presence of immature red blood cells, leukocytosis, a shift to the left, myelocytes, even rare myeloblasts seen, platelets may increase in number, polychromatophilia, Howell-Jolly bodies, anisocytosis, poikilocytosis; in certain cases, however, there may be leukopenia and thrombocyto-

penia; the bone marrow is hyperplastic.

d. Look for bilirubinemia and elevated icterus index.

e. When the degree and rate of blood destruction are very great, hemoglobin is liberated into the plasma and, if the hemoglobin-binding capacity of the plasma is exceeded, free hemoglobin is excreted by the kidneys and hemoblobinuria results. However, the finding of red urine must not be assumed to be necessarily indicative of hemoglobinuria. The color may be produced also by intact red blood cells, porphyrin or myoglobin. Microscopic and spectroscopic examination of the urine will reveal the cause of the abnormal color.

f. More often, blood destruction is less rapid. In such cases hemoglobinemia and hemoglobinuria are not found.

g. The icterus index, serum bilirubin and urobilinogen excretion in the urine and feces are elevated.

h. The van den Bergh is indirect but some increase in direct or "one-minute" bilirubin (bilirubin glucuronide) may also occur.

i. Look for morphologic red blood cell defects: spherocytes, target cells or sickle-cells.

j. Altered red blood cell fragility (always present in hereditary types). The test is generally positive in hereditary spherocytosis and negative in acquired forms with few exceptions.

k. Detection and identification of abnormal hemoglobin (which give rise to hereditary traits and anemias): S, C, D, E, F, G, H, I, J, K.

l. Increased mechanical fragility has been observed in congenital hemolytic jaundice, in sickle-cell anemia, and in the presence of cold agglutinins.

m. Perform test for cold hemolysis.

n. Perform test for warm hemolysin.

o. Perform test for increased acid hemolysis.

p. The Donath-Landsteiner test should be carried out.

q. Ask for "direct" Coombs' test and "indirect" Coombs' test. See Table II.

TABLE II

COOMBS' TEST

Hemolytic disorder	*Indirect*	*Direct with Rh+*	*Indirect with Rh—*
1. Acquired hemolytic anemia:			
a. With circulating antibodies	+	+	+
b. Without circulating antibodies	+	—	—
c. Due to Rh antibodies in Rh+ infant (Erythroblastosis fetalis)	+	+	—
d. Due to physical and chemical agents	±	—	—
2. Congenital hemolytic anemia (Hereditary spherocytosis)	—	—	—
3. Paroxysmal noctural hemoglobinuria	—	—	—
4. Paroxysmal cold hemoglobinuria (type associated with syphilis)	+	—	—

A. Extracorpuscular causes: As far as the first seven causes of hemolytic anemia as listed in Table I (Causes of Anemia) there is nothing more to be added about their symptomatology, except to say that in the presence of signs and symptoms of hemolytic anemia one should look for their presence.

8. Anemias due to immune body reaction:

a. Look for the presence of the virus diseases listed under 8a

b. History of blood transfusion —Signs and symptoms of hemolytic anemia

c. Isoagglutinins anti-Rh: Rh— mother, Rh+ father, Rh+

(Cont. on page 331)

COMMON ERRORS IN THE DIAGNOSIS OF THE ACUTE ABDOMEN*

G. S. SERINO, M.D.**

CASE REPORTS AND STAFF DISCUSSION***

We are cognizant that not only do common errors exist, but that those errors are common to us all.[1] To some degree these errors will continue to exist. However, if one can determine the causes for such errors, the possibility of reducing the incidence becomes more promising. With this thought in mind I have undertaken the task of reviewing a great number of acute abdominal cases which were treated during the past 25 years.

As a result of this survey it is evident that the scientific method is the only one which will insure the making of a proper diagnosis. It also is clear that handling of evidence needs a sense of expertness. Disastrous conclusions frequently are made by the examiner who forsakes the scientific method and, as a substitute, depends on his clinical experience.

What then is the proper scientific method? Making a diagnosis embraces two items: taking evidence and interpreting that evidence. There are three sources of evidence: the history, the physical examination and the laboratory data. All three are important.[2]

Sources of error may be diminished by taking evidence properly. It is necessary that the examiner know the course and natural history of the disease under scrutiny. In addition, he must know various diseases which may give rise to a train of symptoms or a group of findings similar to the entity which is believed to be present.[3] Frequently the case under consideration does not fit any of the classic descriptions of typical disease entities. In such cases knowledgeable weighing and sifting of evidence is important. It may be impossible to clearly identify the exact nature of certain diseases entities without recourse to operation. This is particularly true when the examiner encounters a rare situation such as a ruptured duodenal diverticulum.[5] Difficulties in diagnosis also may arise in a case where a perforated duodenal ulcer with massive bleeding is encountered in the newborn.[6]

To be satisfied with the diagnosis of "Acute Abdomen" robs the endeavor of much of its interest.[7] These "academic errors" are a source of irritation to the mental state of the surgeon alone, but errors which may affect the patient's chance of recovery are of vital concern to both patient and doctor.[8] Fortunately, serious errors are infrequent in modern practice.

Significant reasons for errors in diagnosis of the acute abdomen as revealed by this survey are briefly as follows:

1. Failure by the examiner to obtain a clear and concise history.
2. Failure to evaluate the total individual.
3. Failure in securing necessary and available laboratory data.
4. Failure to recognize the "time factor" —early, advancing and late in the various disease entities.
5. Failure by the surgeon to correlate the facts with established laws of physiology, embryology, anatomy and pathology.

*Red at regular scientific meeting of Staff of St. Francis Hospital on May 27, 1958.

**Chief in Department of Surgery, St. Francis Hospital.

***Participating: James M. Hofford, M.D., Assistant in Dept. of Medicine; Harold A. Tarrant, M.D., Associate in Metabolism; George J. Boines, M.D., Director, Dept. of Medicine; Lawrence J. Jones, M.D., Director, Dept. of Surgery; David J. Reinhardt, III, M.D., Assistant, Dept. of Medicine; Joseph A. Arminio, M.D., Assistant, Dept. of Surgery.

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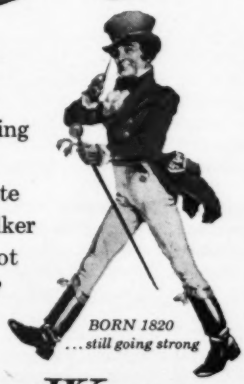

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1. Rein, C. R., Fleischmajer, R., and Rosenthal, A. L.: J. A. M. A. *165*:1821, (Dec 7) 1957.
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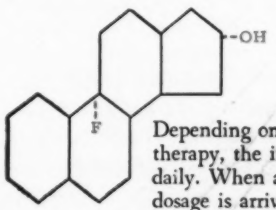

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6. Failure to re-evaluate the patient.
7. Failure to repeat laboratory studies.
8. Failure to evaluate the patient properly due to the masking effects of laxatives, opiates and antibiotics.
9. Failure to realize that the waiting attitude by the surgeon is fraught with disaster.

Many who are taken with abdominal pain in the daytime endure till evening before they feel compelled to send for the doctor. By this time the patient and his family are both showing signs of emotional instability. The physician, weary from the day's work, is physically and mentally below his best. To make important decisions under these conditions is difficult. The temptation often is strong to temporize and "see how things are in the morning." This waiting attitude is understandable, but rarely excusable.

In retrospect, if the above findings were carefully applied in the following cases these errors might have been avoided.

CASE REPORTS

A 28 year old female entered the hospital with the admitting diagnosis of an acute abdomen. The history showed that she had awakened suddenly at 6 a.m. with sharp, steady pain over the epigastrium which shifted during the next few hours to the right lower quadrant. The pain was followed by severe vomiting. She was examined by her local physician who administered an opiate and advised that she be admitted to the hospital.

Past history was essentially non-contributory.

Physical examination revealed temperature, 99.8 degrees; pulse, 96; respiration, 24. The remainder of the physical examination was essentially negative except for the abdomen where tenderness was found throughout, being more marked in the lower right quadrant. There was rebound tenderness in this area with the suggestion of a mass. Muscle rigidity was slight in the epigastric area and more intense in the right lower quadrant. The abdomen was not distended and the peristalsis was hypoactive.

Laboratory test showed hemoglobin, 11 gm.; RBC, 3.3 million cells; WBC, 11,500 with 84 per cent polymorphonuclear leukocytes. Analysis of urine was negative. Roentgenograms of the abdomen and chest were not considered necessary.

These findings suggested the preoperative diagnosis of acute appendicitis. Based on these findings it was apparent that peritonitis of the localized variety was present. These findings also suggested that leakage from this abscess in a cephalic direction was taking place.

Upon opening the abdominal cavity, exploration revealed the presence of undigested food, gastric contents and air. This indeed was an error. This error occurred 25 years ago as I was finishing my internship. My chief, who was noncommittal prior to the surgery, quickly extended his incision upward on finding a normal appendix. The ruptured and leaking duodenal perforation was quickly repaired. The patient made an excellent recovery.

The examiner in this case did not obtain a good history. He was mislead from this poor history into believing that the appendix was the source of difficulty. In a perforated duodenal ulcer the most valuable data for proper diagnosis may be obtained from the history. This catastrophe, which occurs with dramatic suddenness, causes a great and immediate disability. The patient lies prostrate. The face shows signs of pain and anxiety. The flooding of the peritoneal cavity with gastric contents produces excruciating pain and board-like contractions of the abdominal muscles. The signs and symptoms produced by the perforation vary according to the time which has elapsed since the perforation occurred. Physical examination frequently leaves no tell-tale signs. When a patient suspected of having a perforation of a duodenal ulcer is examined several hours after the occurrence of the disaster, board-like rigidity may be absent altogether. Occasionally, as in this case, even as great a rigidity may be noted in the right lower quadrant as over the perforation. This phenomenon is explained on the basis that after the elapse of several hours more fluid accumulates in the right

lateral gutter opposite the appendix than near the perforated duodenum. The gastric juice, which is a potent irritant, excites the peritoneum to pour out a good amount of serous fluid which tends to dilute the irritant.

EVALUATION

The first source of error was directly responsible for negligence concerning the necessary laboratory work and x-ray observance of the abdomen. This laboratory aid plus a good history might well have solved the diagnostic problem. This error, however, did not adversely affect the patient's chance of recovery. The signs and symptoms produced by a perforated duodenal ulcer vary according to the time which has elapsed since the rupture occurred: (1) The stage of prostration or primary shock. (2) The stage of (advanced) frank peritonitis and secondary shock. (3) The stage of reaction (with masked peritonitis). There is no hard-and-fast limit between the stages. It is during this stage of masked peritonitis that many capable observers have been deluded into postponing surgery. The intensity of the initial shock subsides, and the patient then looks better and feels more comfortable. The circulatory system recovers to such an extent that the extremities may become warmer, the face normal in color and the pulse normal in frequency and strength, while the temperature is normal. The improvement of symptoms does not imply any cessation of the pathological process though the casual observer might easily think that real improvement were taking place. Nor is the patient's own opinion of his condition always to be trusted for he often expresses himself as "feeling much better," and he may even begin to think lightly of his condition. But his attitude and his actions belie his words. Upon the proper appreciation by the doctor of this dangerous latent period depends the patient's chance of recovery from his disease. It is at this period that the favorable opportunity for operation passes.[9]

CASE REPORT #2

A 30 year old female entered the hospital with an admitting diagnosis of an acute abdomen. The history was that of having developed crampy abdominal pain in the epigastrium about 8 a.m. The pain localized to the left lower quadrant at 11 a.m. Nausea and vomiting developed shortly afterward. She called her physician at 11:30 a.m. She was examined and advised to enter the hospital.

Past history revealed that she was delivered of a normal baby four weeks previously. She remembered having similar pain six weeks prior to her delivery. The pain lasted just a few hours, mild nausea was present and she thought this was due to the eating of potato chips.

Physical examination revealed a well nourished white female. She gave little evidence of being acutely ill. Sitting up in bed she announced that she "felt very well." Temperature was 100.4 degrees; pulse, 102; respiration, 20. The remainder of the examination was negative except for the abdomen where tenderness was found throughout, being much more marked in the left lower quadrant. There was rebound tenderness in this quadrant with definite muscle rigidity. The abdomen was neither scaphoid nor distended and the peristalsis was hypoactive. Vaginal and rectal examinations were essentially negative.

The blood count showed 13 gm. of hemoglobin with 4.1 million red blood cells; 20,900 white blood cells with 88 percent polymorphonuclear leukocytes, 8 percent lymphocytes and 4 percent monocytes. Urine analysis was essentially negative. Roentgenograms of the abdomen and chest were non-contributory. It was established that the patient was suffering from peritonitis due to a perforated diverticulum of the sigmoid colon and operation was decided upon.

Upon opening the abdominal cavity, exploration revealed the presence of cloudy fluid. An acute appendix was found plastered to the sigmoid colon on the left side.[10] The tip of the appendix had perforated over the colon forming an abscess. Appendectomy without drainage was performed. Convalescence was uneventful.

EVALUATION

This error was long remembered because in 1946, and again in February, 1958, two similar cases were admitted to the hospital and the correct preoperative diagnosis in each case was made by this observer. It is apparent that in the above case the error was not due to a poor history. In fact, the historical sequence of events from a sign and symptom standpoint were perfect with slight variation from the normal: (1) epigastric pain and left iliac localization instead of right iliac localization; (2) vomiting, nausea, but no acute loss of appetite; (3) presence of local deep tenderness; (4) presence of muscle rigidity; (5) presence of slight fever; (6) increased white cell count; (7) negative roentgenograms. In this case the history, physical examination and the necessary laboratory aids were in perfest order. The anatomical and physiological criteria for proper diagnosis seemed to be in good order. What then was the source for error? The error was due to the failure to apply the known laws of embryology concerning rotation of the bowel. The lack of fusion of the peritoneal coats produced the condition known as "mobile cecum." Many, if not most, of the mistakes made in the diagnosis of appendicitis were due to a failure to realize the great difference in signs and symptoms which follow from the varying positions and relations of the appendix.[11] The appendix, though usually described as being situated behind the ileocecal junction with the tip directed towards the spleen, is not always found in that situation when it is diseased and sought for by the surgeon.[12]

Every clinician knows that the presence of general abdominal pain, nausea and vomiting with localizing right lower quadrant pain and tenderness points to the acute appendix. Yet not always does the appendix clamor so clearly or in so straightforward a fashion for its removal.[13]

THE PELVIC APPENDIX

Another dangerous position of the appendix is the pelvic appendix. In this position the early symptoms of an attack of appendicitis when the appendix is situated in the pelvis are similar to those which ensue when it is situated above the pelvic brim, with the exception that the rigidity of the abdominal wall is seldom present in the early stages and pain is more frequently felt in both left and right iliac areas. Pain is not so readily localized in the right iliac fossa but is always felt on deep pressure at the brim of the pelvis and the epigastric pain may dominate for a longer time. The perforated pelvic appendix is easily overlooked and, therefore, one of the most dangerous conditions which may occur in the abdomen.[14] The reason appears to be as follows: While the appendix is not perforated but swollen and tense, the pain caused by distention and peristalic contraction is definite and severe and is felt chiefly in the epigastrium or umbilical area. When perforation occurs the epigastric pain diminishes and local pelvic peritonitis results. This usually is unaccompanied by rigidity of the lower abdominal muscles. When perforation occurs the pain of appendicular disease ceases, the epigastric pain diminishes and local pelvic peritonitis results. The pain due to pelvic peritonitis at this early stage frequently is insignificant, the patient may seem better and physical examination of the abdomen may give the examiner little indication of trouble in the pelvis. Usually within a few days either the peritonitis becomes definitely localized into a pelvic abscess or the inflammation may track upward, frequently along the sigmoid colon, towards the general abdominal cavity. This will give rise to increasing pain, distention and rigidity of the abdominal wall.

Fortunately, the mortality from appendicitis has been reduced during the past ten years almost to the vanishing point.[15] There are many reasons for this improvement.[16] The two most important factors deal with the problem of the medical advisor and the public as a whole. The modern doctor has a greater appreciation of the early signs and symptoms of appendicitis.[17] As a result, we surgeons see today very few cases of late appendicitis. The second reason relates to the courage, intelligence and understanding of the medical profession in discharging its public responsibilities. If you will permit one commercial, let me say,

"It pays to advertise." Never, perhaps, in the history of our nation has a system devoted to "education of the public" paid such rich rewards.

CASE #3

A 42 year old obese white male entered the hospital on March 18, 1958 with the admitting diagnosis of an acute abdomen. The history was of having awakened suddenly on March 16, 1958 at 5 a.m. with sharp, crampy pain in the right lower quadrant of the abdomen. He went to the bathroom and took a dose of an alkaline analgesic. Several hours later he vomited and since the pain continued he called his family doctor who sent him to the hospital for laboratory tests. Investigation of the abdomen by roentgenogram was negative. The WBC was 22,100. Urine analysis showed a two plus albumin and marked microscopic hematuria and pyuria. He was treated at home and again admitted to the hospital on the third day of his illness.[18] There was radiation of the pain to the lumbar area at this time but no other urinary symptoms except frequency was present.

Past history was essentially non-contributory, and revealed nothing which would lead one to suspect the actual disease that was present.

Physical examination revealed a flushed, obese white male, appearing acutely ill. Temperature was 102; pulse, 106; respirations, 22; blood pressure, 150/82. The remainder of the physical examination was essentially negative except for the abdomen where tenderness was found throughout the lower abdomen, being more marked in the right lower quadrant. Muscle rigidity also was present over this area. The abdomen was rotund but slightly distended. Peristalsis was hypoactive. Rectal examination was negative for blood, pus, mucous, growth or tumor mass.[19] Laboratory tests were essentially the same as that of March 16, 1958.

It was felt that the patient was suffering from some sort of kidney disease complicated by a localized peritonitis. The peritonitis might be due to a perforated appendix lying behind the ileum. Operation was decided on with a preoperative diagnosis of acute appendicitis with perforation.

The abdominal cavity was entered through a right lower quadrant transverse incision. The appendix looked normal. The sigmoid colon was found in the right iliac fossa. The lower portion of the omentum which was acutely inflamed was found glued to this portion of the sigmoid colon. The omentum was peeled from the colon disclosing multiple perforated diverticuli. A prophylactic appendectomy was performed followed by the colonic surgery. Convalescence was uneventful.

In diagnosing acute abdominal disease it is always necessary to exclude medical diseases. There are a number of diseases which do not need or positively contraindicate operative interference.[19] Was this such a case? Interpretation of the existing facts led the observer to conclude that he was dealing with two separate and distinct diseases, one of which required an immediate operation. The examiner fully appreciated the well known fact that acute abdominal disease with genito-urinary organs or to secondary irritation of those organs. A diseased appendix lying over the right ureter or in front of the renal pelvis may cause trouble in the diagnosis. He was also aware of the fact that small ureteric calculi do not always show on a roentgenographic film. The decision to defer further pyelographic studies seemed justified. The failure to identify the exact pathology[20] was again due to the failure to think in terms of anatomy and embryology.[21] To have kept in mind the fact that a long and redundant sigmoid colon may be found in the right lower quadrant of the abdomen might have produced a rather brilliant preoperative diagnosis.

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DISCUSSION

Dr. James M. Hofford: When one thinks of an acute abdomen and whether an operation should be performed, several categories come to mind. Appendicitis, acute gall bladder disease, acute pancreatitis, perforated peptic ulcer, intestinal obstruction (of small or large bowel) and acute gynecological disease are some of these.

Appendicitis is frequently and should be kept first in mind. Re-evaluation of this type case is often needed, and by a careful follow-up diagnosis can be made. The atypical location of the appendix, for instance the pelvic type, might give a bizarre group of subjective and objective symptoms and signs. A rectal examination should always be done and tenderness looked for in all cases of abdominal disease.

A chest x-ray and flat plates of the abdomen should be made in cases of acute abdominal pain, especially before operation. Hematuria may confuse the diagnosis of appendicitis. This may come from nephritis or from an appendix irritating the bladder wall or ureter. Sometimes intravenous pyelography is necessary to be definitive.

An acute upper respiratory infection is associated with a mesenteric adenitis. Usually, a mesenteric adenitis will improve within six hours with antibiotic therapy.

The House Staff should remember that sometimes patients develop appendicitis in the hospital, with or without a prior disease history. People treated for ulcers sometimes develop fecaliths which lodge in the appendix. An x-ray might show calcium in the appendix.

All patients receiving cortisone should be suspected of having a perforated ulcer. Cell tumors of the pancreas must be distinguished from perforated duodenal or jejunal ulcers. The latter must be kept in mind, especially when a patient has had gastroenterostomy or previous surgery.

Acute gall bladder disease is always in the mind of the surgeon. The blood count is usually much higher than in appendicitis especially if empyema is developing. Occasionally, in an acute gall bladder which ruptures, the cystic artery will also break down and have sclerotic changes and intraperitoneal hemorrhage may occur. Since death from rupture of the gall bladder is high, it is not wise to procrastinate too long if one is in doubt about the diagnosis. Serum amylase and serum lipase should be done in doubtful cases of upper abdominal pain. With acute pancreatitis the amylase often ranges between 1200 and 6000 units, but sometimes the amylase is elevated in perforated peptic ulcer and intestinal obstruction. Occasionally, it may be elevated in acute appendicitis and cholecystitis. The statement is made that in appendicitis perhaps the amylase is elevated because of amylase-producing organisms in the intestinal tract. Following an attack of pancreatitis the patient may develop a pseudo-cyst of the pancreas. This must be watched because it may perforate or obstruct the duodenum.

When intestinal obstruction is suspected one frequently thinks of carcinoma, diverticulitis and volvulus. A practical point of diagnosis is fecal impaction, especially in older people. Since the x-ray is not always positive early in intestinal obstruction the flat plate should often be repeated after 4, 8, or more hours.

IMPORTANCE OF RE-EXAMINATION

The secret of making a diagnosis in acute abdominal disease is to re-evaluate the patient periodically. This is especially true in intestinal obstruction. Adhesions, omental bands or intussusception may occur. More rarely, tumors of the small intestine, simple or malignant, may confuse us. If a tumor of the small intestine is suspected inserting a decompressing tube, such as the Miller-Abbott tube, and passing a little barium down the tube might help in the diagnosis. Foreign bodies in the small intestine may produce obstruction, as one author described due to a piece of undigested steak.

Ileus due to gall stones is not as uncommon as suspected. If the stones are 2.5 cm. in diameter or greater, they can readily cause an obstruction. If less than that they often pass through, and can be found in the bed pan. Air may be seen in the gall bladder or in the bile ducts because these patients have passed the stones by way of cholecystoduodenal fistula.

Even a large bolus of worms may obstruct the intestine. Of course, one must always be on the look-out for hernia as a cause of intestinal obstruction. Omental infarction should always be thought of. Some cases have been reported with torsion of the omentum and some without.

An excruciating pain in the upper part of the abdomen and board-like rigidity, with or without a prior history of abdominal distress, might suggest a perforated ulcer. Here, the x-ray is a valuable aid, because you often see free air under the diaphragm to the right or left. When the x-ray does not show air it might help to pass a Levine tube, removing the stomach fluid. Once this fluid has been removed air may pass through the site of perforation and the x-ray can be repeated. A lateral decubitus film also may be of value so gas may be seen under the right side of the diaphragm.

After 24 to 72 hours suffering with an acute ulcer the patient may go into a state of severe shock. Then the symptoms of chemical peritonitis arise and mask the original diagnosis. In this case, the abdomen may be soft and may be confused with a coronary occlusion.

Some cases of perforated ulcers may be treated conservatively if the perforation is mild. These cases may be treated with Levine tube suction. Some other patients with perforated ulcer may spill the intestinal or gastric contents along the right side of the abdomen, and pain in the right lower quadrant with rigidity might suggest appendicitis. If the error is made and the appendix brought into view, it is important to open the appendix and make sure the large inflammatory mass surrounding the appendix has its origin there. If one is not sure, then the duodenal and gastric regions should be checked for perforation.

Diverticulitis is becoming more common in the large bowel and perforating carcinoma of the large bowel can stimulate appendicitis. Helpful here is the presence of anemia and blood in the stool. A pelvic examination should be done in the case of all female patients. Frequently, with a twisted ovarian cyst there may be an associated paralytic ileus.

Rupture of the graafian follicle at the mid-stage of the menstrual cycle may confuse the doctor. Pneumonia may result in abdominal distention and the chest should be gone over carefully in all cases. An electrocardiograph should be taken with a careful heart history. Herpes zoster in the prevesical stage can be confusing and cause abdominal pain. Sickle-cell anemia in colored people gives abdominal pain. Diabetic acidosis has often been confused with appendicitis. Porphyria may produce abdominal pain. Palpation of the abdomen by the surgeon before operating may reveal conditions which were present before.

An interesting abdominal problem is hydatid cyst. A case of this type was reported in a 60 year old lady who had been to the Near East. While there, 20 years ago, her main companion was a dog. Recently she developed an upper abdominal mass which pressed the colon downward. She was found to have a large hydatid cyst. Sheep and dogs frequently help in the transmission of the coccus which produces hydatid cyst.

One should try never to spill the contents of a cyst. It should not be needled because it can spread the disease in the abdomen.

To go to the extreme, a 10% solution of fructose given in 20 minutes has been reported to cause severe abdominal pain. One must watch for hepatitis with abdominal pain. A case was reported recently from the administration of chloropromazine which caused a hepatitis followed by abdominal pain.

Rupture of an aortic abdominal aneurysm must be kept foremost in mind. There are three signs to look for: flat plate of the abdomen shows absence or lowering of the solar shadows; the patient may show a loss of patellar reflexes or lower abdominal reflexes, ecchymotic spots may be found on the extremities and in the perineum.

Acute abdominal disease can be a research project in itself.

Dr. Harold A. Tarrant: I have been asked to discuss a case of a 47 year old widow who had complained of obstipation for a period of several days and had had advice from a local physician with a specific request that the patient keep in contact with the doctor daily, noting her progress. Apparently, from the history given she became progressively worse over a weekend and did not call her family physician, but instead was taken to one of the local hospital emergency rooms by her son for examination, diagnosis and treatment.

The intern was told that the patient was unable to pass gas, that she had had no bowel movement for three or four days, that she was experiencing abdominal pain, intermittent in character, dull to sharp and some abdominal distention. At the time of examination she had no temperature but did have abdominal distention and her family was told that her trouble was constipation. It was recommended that the patient be taken home and given a laxative and an enema. If this did not relieve she was to contact her physician. Unfortunately, no rectal examination was made, nor was there any blood count done.

These orders were carried out by a relative and, after the enema was given, some abdominal pain was noted in the right lower quadrant. The patient became progressively worse and a local physician was called to examine the patient at home. It was obvious that she had an acute intestinal obstruction. An opiate was given and she was admitted immediately to a local hospital for hydration and surgical opinion.

On admission she had an elevated temperature, leukocytosis, abdominal distention with absence of peristalsis and a palpable mass in the right lower quadrant. The surgeon was of the opinion that she had an intestinal obstruction. He recommended that she be subjected to surgery and a laparotomy be done immediately.

At the time of surgery there was evidence of an intussusception with a sizeable area of gangrenous colon which was resected, and although the patient had a stormy convalescence she did recover. Unfortunately, she later developed many sequelae which required further surgery.

This case has been presented briefly to draw to the attention the fact that it is important for interns and residents to have supervision by chiefs on the services in order that opinions may be obtained, and that these cases may receive suitable care to the best interest of all parties concerned.

Why are we missing the diagnosis in these cases? Are we taking incomplete histories, or placing too much emphasis on negative or atypical laboratory findings? Perhaps we are sometimes over-conservative in our attitude toward surgery and need to evaluate our criteria for performing exploratory surgery.

Dr. Joseph Hughes: I would like to say something about acute appendicitis. The surgeon often decides to operate because the patient is sent in with a diagnosis of acute appendicitis. After the patient is admitted to the hospital the surgeon should follow through with all the known methods of examination and rule out the obvious things that could present similar symptoms. Renal calculi, pelvic inflammatory disease, and pneumonia should be ruled out. This

is best done in cooperation with the family doctor or internist. If, by a process of elimination, he has ruled out most of the differential diagnoses, then I think he is justified in going ahead and operating on the patient.

Here again, the surgeon is on the spot if he removes a normal appendix. He is then subject to the criticism of the tissue committee, which is a necessary committee in every well run hospital. Johns Hopkins Hospital recently put out a report which was presented in one of their conferences. They claim to remove 15% to 25% of appendices in which the specimen does not show any acute pathology. Fortunately, I was able to talk to the doctor concerned with this report and he says that this is similar on both the ward service and the private service. He justifies that it is better to operate on a doubtful case, especially when rupture, gangrene, abscess and peritonitis can be avoided. This is particularly so in children.

I do feel, however, that the tissue committee should invite the doctor concerned with such a case to appear before them and present his case and also present it before the surgical departmental meeting. By doing so, and going over the methods of his diagnosis and his management, it would be possible to improve on the diagnosis in future cases.

Dr. Lawrence J. Jones: The diagnosis of appendicitis is very difficult to make and to differentiate from other causes of the acute abdomen. Recently, I saw a young girl, 15 years of age, who was tender over McBurney's point. I thought she had a regional lymphadenitis but the family was insistent on operation. This I refused to do. The abdomen quieted down and the patient went back to school. Later, I heard that she had had another attack and her appendix was removed in a hospital close to her school. Evidently she had appendicitis.

Dr. David J. Reinhardt: May I comment on Dr. Serino's paper concerning the part in which he discusses the EKG in a case of acute pancreatitis? One should be able to make a differentiation between the abnormal cardiogram in this case and a cardiogram which is diagnosed acute myocardial infarction. Exceptions may occur. For example, the patient with pancreatitis or some other abdominal disease may have had an old coronary and have Q-waves and other changes which might be confusing. In a case like this, it is very helpful to know the previous history and to have a baseline cardiograph in all patients.

Dr. Joseph Arminio: In reference to tissue committees, if one is on this committee he must assume a certain amount of responsibility and take a certain amount of criticism, just or unjust. Of course, the important thing to do after an operation is for the surgeon to put his findings in writing. That is the one thing which I think all of us have heard from medical school to internship. If we were all a little more diligent in writing down more explanations of our actions in diagnosis and treatment the patient would be better off and so would we. A positive diagnosis is pretty straightforward and often needs little comment, but the ones that aren't straightforward should have more important details written down about them. This should contain a great deal of thought. The tissue committee has little difficulty with cases that are well written up.

Dr. George Boines: The medical man has as much difficulty as the surgeon in diagnosing the acute abdomen. To support Dr. Serino's statement about the ease of error in such diagnoses, I wish to relate to you a few cases.

A patient, age 56, male, white, was complaining of abdominal cramps. He was admitted to the hospital on March 3, 1958. I.V. pyelograms showed bilateral double kidneys and ureters. He was discharged. On May 12, 1958 he was readmitted for a painful abdominal mass. Surgery showed ruptured diverticulum with adenocarcinoma of the transverse colon.

The next case, a female, age 44, white, who complained of pain in the right upper quadrant with all the clinical evidence of gall bladder disease. X-rays showed poor function of the gall bladder but no stones.

The surgeons did not feel the clinical findings were sufficient to operate. The patient thought she had gall bladder disease because her father was operated and found to have cancer of the gall bladder which had perforated. The daughter insisted on operation. She was found to have a cholecystitis, and the gall bladder was removed.

The next patient was age 19, white female, who complained of pain in the right lower quadrant and had had several attacks since 1956. She was admitted to the hospital on July 21, 1957 and diagnosed as pelvic inflammatory disease. She was sent home with this diagnosis. However, she was readmitted to the hospital on January 8, 1958 and was operated on for appendicitis. A retrocecal appendix with pus was found; normal ovary and tubes were found.

A female, age 24, white, was hospitalized for acute pain in the lower right quadrant. At this time, she was four months pregnant. She was hospitalized five times in 1953 by other physicians for similar abdominal pain. Her blood count and temperature were normal. For this reason, surgeons did not feel that there was an indication to open her abdomen. Conservative treatment, therefore, was instituted. However, on a hospital admission on August 8, 1954 she was operated and an appendix attached to the posterior parietal wall was found surrounded by an abscess.

Dr. G. S. Serino: Not only a good history is necessary, but also a good examination. Certainly a distended, enlarged abdomen should never be missed and the younger doctors, as well as the older, should look over every abdomen very closely especially if there has been a history of recent vomiting. However, the most difficult and dangerous case is the flat abdomen which has a hidden obstruction.

Some doctors maintain that changes in the cardiograph in cases of acute pancreatitis were of the type that might occur in acute myocardial infarction. However, I am glad to hear that Dr. Reinhardt thinks that such cardiographs can be distinguished from acute myocardial infarction, especially with the aid of the serum transaminase test.

In reference to Dr. Boines' questions, I do agree that sometimes we have incomplete histories; the sicker the patient, the more detail should be gone into. In reference to laboratory findings, I think we should use them as an aid to our clinical observations and not use the laboratory as the sole guide. Sometimes this takes a great deal of maturity to develop the judgment to add the link of the laboratory chain to the other subjective and objective symptoms and signs. This is where consultation comes in, especially in those cases where judgment is the only thing that will bring better diagnosis.

I think it is true, as Dr. Hughes brought out, that occasionally a prophylactic operation for appendicitis or a prophylactic abdominal exploration may have to be done. Sometimes when the family doctor or internist is not sure, and valuable time is being wasted, it is better to do surgery while the patient is in good condition. The margin of error of 15% to 25% is justified by the avoidance of the greater mistake of missing a gangrenous peritonitis, for example.

MALIGNANT URETERAL TUMOR (CASE REPORT)

BRICE S. VALLETT, M.D.*

The purpose in reporting this case of malignant ureteral tumor is to point out the variety of attack necessary at times in achieving palliation and sometimes a cure. Experience has shown that the malignant papillary type tumors of the ureter are more amenable to therapy than the malignant non-papillary type which usually has a fatal outcome.

A white male, 60 years of age, was admitted to St. Francis Hospital on July 20, 1954 for diagnosis and relief of painless hematuria with blood clots. Six months prior to admission he had passed some reddish urine for which a private physician had prescribed medication. His general health had always been good. One sister had died from cancer.

Cystoscopy July 20, 1954 revealed a papillary type tumor surrounding and involving the left ureteral orifice. On July 21 an excretory urogram revealed no function of the left kidney. The right pyelogram was normal. On July 22 endoscopic vesical neck resection of the tumor was carried out and eight platinum radon seeds (2.5 mc. each) were implanted in the bladder wall at the site of the tumor base. On August 30, 1954 the left ureter was catheterized and a large hydronephrosis of the left kidney found on pyelography with a filling defect of the lower pole. Urine from this kidney had not revealed any cells suggesting malignancy.

September 2, 1954: Left nephroureterectomy and segmental resection of the bladder wall, including the area of the left ureteral orifice and former bladder tumor site, was carried out.

The pathologic diagnosis was transitional cell carcinoma of the ureter (Grade I) and hydronephrosis.

January 16, 1957: There was recurrence of the bladder tumor and endoscopic resection and electro-coagulation was again carried out. However, it was apparent that there was still inaccessible tumor remaining on the anterior bladder wall. The resected tissue was classified as Grade II transitional cell carcinoma.

January 22, 1957: Suprapubic cystostomy was done with electro-coagulation of all visible tumor tissue. Some of this tissue was classified as Grade III transitional cell carcinoma.

June 25, 1957: There was recurrence of tumor, especially on the anterior bladder wall, only a part of which was accessible to cystoscopic electro-coagulation. Some of this tissue was examined microscopically and classified as Grade I transitional cell carcinoma.

July 5, 1957: A "radium catheter" was introduced through the urethra into the bladder and allowed to remain until July 9 when it was removed. On July 23, this maneuver was repeated, the catheter being removed on July 27.

January 8, 1958: There was no evidence of any tumor recurrence in the bladder. There was some evidence of "radium cystitis." However, the patient was singularly free of complaint referable to his bladder or to urination.

COMMENT

While it is too early to claim a cure for this case, W. W. Scott[1] has stated that "it would seem from the records that any patient who has no evidence of tumor four years or more after operation has a fair chance of being cured."

As ureteral tumors metastasize early, it is imperative that early diagnosis be made. All bleeding from the urinary tract should have adequate evaluation. Hydronephrosis in individuals over 50 years is always suspect for ureteral tumor. The Papanicolaou

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stain of the urine is an invaluable aid in diagnosis in early cases. Jarrett[2] reported this as the only positive finding in an early transitional cell carcinoma (Grade II) of the left ureter. Complete nephroureterectomy was done in November 1955, and this patient is alive and well four years later.

In children ureteral tumors are exceedingly rare and when they do occur are usually benign. Leader[3] diagnosed a ureteral tumor in a 12 year old boy. The "circle sign" of Nesbit was present on ureteral catheterization and at operation the left kidney was found to be normal. One centimeter below the ureteropelvic junction the ureter was dilated and on gentle palpation thought to contain a solid tumor mass. A two centimeter segment of the ureter containing the tumor and one centimeter of the distal renal pelvis was resected and submitted for frozen section. The tumor proved to be a fibromatous polyp.

SUMMARY

1. A case of malignant papillary carcinoma of the left ureter is reported with no evidence of recurrence after four years.
2. Recurrent tumor of the bladder was observed as long as three and one half years after removal of the ureter tumor.
3. The Papanicolaou stain of centrifugalized urine aids in detecting early malignant changes in the urinary tract.
4. Ureteral tumors in children are usually benign.

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(Cont. from page 319)

child, Coombs' test as shown in Table II

d. Paroxysmal cold hemoglobinuria (Note: The term paroxysmal hemoglobinuria [some authors talk of "hemoglobinuria" instead of paroxysmal hemoglobinuria] refers to sudden intravascular hemolysis followed by hemoglobinemia and hemoglobinuria. Several closely related clinical syndromes are included under this heading, i.e., paroxysmal cold hemoglobinuria in lues, paroxysmal nocturnal hemoglobinuria, also called Marchiafava-Micheli syndrome, March hemoglobinuria, cold hemoglobinuria in primary atypical [viral] pneumonia, and on rare occasions in other viral and rickettsial infections.) Paroxysmal cold hemoglobinuria is an uncommon disorder, characterized by sudden passage of hemoglobin in the urine, following local or general exposure to cold. Aching and pain in the back, legs or abdomen and other symptoms of acute hemolysis, such as chill, fever and malaise, are associated with the passage of dark brownish urine. Other findings are those characteristic of acute hemolysis.

Summary for study of a patient with a hemolytic disorder: Hemolytic anemia can be recognized by the development of certain symptoms and signs, certain changes in the blood and bone marrow and characteristic alterations in hemoglobin and bilirubin metabolism as already outlined. The differentiation of the various hemolytic disorders is important since treatment depends on their nature.

End of Part I

(To be continued)

THE HOMEOSTATIC CONTROL OF THE FEASTING BLOOD SUGAR

EDWARD M. BOHAN, M.D.*

Medical interest in the feasting blood sugar has increased rapidly. It is being used to some degree in all Wilmington hospitals. On the metabolic service at St. Francis Hospital and on all medical non-diabetic patients on medical service, it is used as a routine test on admission of the patient.

Sindoni[1] originated medical literature on the subject as early as 1939. In 1946 he[2] published material on a series of cases not diabetic, which had feasting sugars one-half to four hours after a test meal. This test meal consisted of 32 grams of protein, 64 grams of fat and 96 grams of carbohydrate. This was a breakfast-type meal. At no time following the meal did the blood sugar rise above normal.

In order to understand this phenomenon one needs to think in terms of homeostasis of the glycemic level of the blood. Soskin[3] describes this physiological principle in a masterful fashion.

Many writers[4,5,6,7,8] still quote the feasting blood sugar at a height of 140 mgm. to 170 mgm. per 100 cc. of blood and say that the physician should suspect diabetes if the blood sugar exceeds these levels. In the first place, only a person with deranged carbohydrate metabolism will run a sugar over 140 to 170 mgm. per 100 cc. of blood. Secondly, no normal person will exceed 120 mgm. feasting at any hour following a meal.

The meal tolerance test of Sindoni[2] does not place the same stress on the homeostatic mechanism of blood control that the 50 or 100 grams of glucose does. There is much faster absorption of plain glucose with a rise as high as 150 to 180 mgm. per 100 cc. of blood.

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The meal tolerance does not cause a rise this high. It has been proven to be not higher than 120 mgm. per 100 cc. of blood at any time following the meal by the actual records of hundreds of cases performed routinely on my office patients and hospital patients known to be non-diabetic.

However, if the patient is diabetic the post-prandial sugar will be elevated or if a temporary derangement of carbohydrate metabolism occurs, as in coronary thrombosis, cerebral vascular accident or administration of intravenous or oral glucose, then the feasting sugar will be elevated but this is not due to diabetes.

This knowledge of what disturbs the homeostatic control of the blood sugar enables us to use the feasting sugar as a diagnostic aid. Any blood sugar known to be laboratory accurate over 120 mgm. per 100 cc. of blood should be investigated for the possibility of diabetes mellitus.

Is the post-prandial *capillary* sugar accurate? Does it exceed the *venous* sugar taken at the same time? Evidently there is very little difference between the capillary and venous results—vide infra.

Soskin[9] points this out in quoting Cavett and Seljeskog. They made a comparison of the reaction of sugar tolerance curves to 50 grams of glucose given by mouth. Simultaneous capillary and venous testing was performed in these non-diabetic subjects.

The capillary curve ran very slightly higher than the venous throughout the test but both venous and capillary curves were exactly similar in course in these non-diabetic subjects.

Therefore, it can be assumed that capillary and venous blood sugars are so identi-

cal following the meal tolerance test that the results can be interchanged for all practical purposes.

More data on capillary feasting sugars was supplied by Orent-Keiles and Hallman[10] who estimated capillary sugars on this feasting basis in 1949. They gave 56 volunteers eight different food combinations, ranging from a cup of coffee to a breakfast containing 758 calories. Capillary blood sugars, using the Folin-Micro method, were taken at one-half to three hours after these various types of meals. Results were obtained at one-half hour intervals.

The maximum two-hour rise in the whole series was up only 23 mgm. from the fasting. In other words, the fasting blood sugar was 79, and the feasting blood sugar, 102. This was the maximum single rise, not the average. The average of the whole 56 cases was only 8 mgm. above the fasting level; exceeding 120 mgm. feasting on one occasion (127 mgm. per 100 cc. of blood).

In May, 1951, Ackerman and Bohan[11] published a verification of Sindoni's original work.

Gerber, Bove, and Macy[12] at the Philadelphia General Hospital also have substantiated the above findings in their clinical work and writings.

At St. Francis Hospital, we have picked for this paper 100 random cases of 2 hour post-prandial sugars on known non-diabetics. In my office, I have performed post-prandial blood sugars as a routine check for the past 13 years. The results of the hospital and 50 office cases are in the table at right.

Believing that the post-cibal sugar exceeds 120 mgm. in non-diabetics is, therefore, a medical fallacy. In discussing the culture of the Middle Ages, Hayes and Moon[13] noticed that there was a tendency for medieval scholars to derive their notions of science not from personal observation and experiment, but from books. What our teachers have taught us, we are inclined to believe. Respect for teachers we must have, but all is not verity in the classroom or lecture hall. One must sift the grains of sand to find the gold. Search for truth then becomes research.

FEASTING BLOOD SUGARS*—
(TWO HOURS)

1957

HOSPITAL PATIENTS					OFFICE PATIENTS	
85	96	80	83	95	92	82
80	104	85	104	85	86	93
115	90	93	100	80	69	106
					108	
81	107	100	100	98	114	98
					118	
76	104	100	125	76	88	112
					112	
123	120	99	96	93	81	104
					85	
86	91	95	76	79	90	96
					70	
87	110	100	102	95	82	88
					83	
90	119	80	83	117	76	90 87
110	79	81	99	98	90	104

1958

HOSPITAL PATIENTS					OFFICE PATIENTS	
80	95	95	95	96	78	98
100	108	88	93	80	89	116
125	92	85	88	79	90	102
104	100	95	85	80	98	86
82	110	85	95	74	117	86
116	100	78	85	83	113	109
87	79	95	78	79	114	83
80	79	96	95	80	82	80
73	109	111	96	100	89	120
80	95	95	111	82	88	114
					86	118
					117	

*Venous method

Sindoni emphasized in 1939[14] that "It is most important to examine the blood for sugar because of the significance and accuracy of the information it gives, as to the true state of the diabetes. Urine sugar control of diabetes is inaccurate, because it depends on the renal threshold which varies with many factors." If this is true, and the evidence supplied by Sindoni is great, then one should use the blood sugar more often as a control in the management of diabetics.

Knowing the feasting sugar level of 120 mgm. per 100 cc. of blood is top normal, then one may use the fasting and feasting

sugar for the control of diabetes. The feasting sugar also may be used as a more accurate method of diagnosis.[15]

Capillary sugars can be used for diagnosis and treatment in the office, in the patient's home or in the hospital. Capillary screening sugars can be performed on the hospital floor if one wishes to use a kit. This is good for an eight-minute bedside level. While it does not give the exact reading, it enables the nurse and doctor to intelligently avoid extremes of glycemia while a patient is under treatment for acidosis, coma or simply stabilization.

SUMMARY

1. The feasting blood sugar in the non-diabetic does not exceed the fasting at any time after an average meal.
2. The homeostatic regulation of the feasting blood sugar is dependent on the liver. This organ pours sugar into the blood prior to the administration of food. It then apparently ceases to do so when food is given and starts to store sugar.
3. Therefore, the feasting blood sugar never rises above the top fasting level of 120 mgm. in the non-diabetic.
4. Capillary sugars seem to vary slightly from venous sugars. One wonders whether they might be used interchangeably in diagnosis and treatment of diabetes mellitus.
5. Sindoni originated the feasting-sugar normal level. After 13 years' observation of his work, and that of Gerber, Bove, and Macy, I am convinced of the feasting sugar level described above.
6. 150 cases of feasting sugars on hospital and office non-diabetic patients are quoted by the author. The maximum venous sugar reached 123 mgm. per 100 cc. of blood on only one occasion. The average was well below 120 mgm. per 100 cc. of blood.
7. A feasting venous sugar over 120 mgm. per 100 cc. of blood should be considered diabetic unless proven otherwise. Joining this knowledge with a family history of diabetes and a glucose tolerance test will result in more accurate diagnosis of diabetes mellitus.

ACKNOWLEDGMENT

Thanks to Miss Ann Moran, R.R.L. for her assistance in compiling and arranging this article and other articles of the St. Francis Hospital's issues in the Delaware State Medical Journal for 1958.

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✚ *Editorials* ✚

SERVICE ABOVE SELF

On October 31st a man died in the city of Wilmington. This man probably was not known by name to other than a few members of the medical profession. His works, on the other hand, were known to most of us.

This man had retired as a grocer more than ten years ago because of his health. He had suffered a severe heart attack many years ago and his physicians had advised him that he must limit his activity strictly if he were to survive. Following his heart attack, he had severe bouts of angina which were brought on by the slightest exertion. Despite this, he devoted two days a week, without compensation, to helping patients at the Veterans Hospital. We all know the Gray Ladies of the American Red Cross. This man was the only male Gray Lady in the State of Delaware. He instructed patients in certain crafts such as belt weaving as a form of diversion during their convalescence. Far more important than this, however, was the manner in which he imparted his optimistic philosophy to all those with whom he came in contact. Three years ago he suffered a thrombo-embolic accident to one of his major blood vessels. This did not stop his activity except for a brief time. Over the past twelve years, he kept up this program by spending a day in bed after each visit to the hospital.

Jim Arieff will be greatly missed by the few of us who knew him personally; his good works will be missed by many who knew only his results.

MEDICAL WRITING

A physician could be one of the best trained men in the world and yet be ineffective because he is unable to transmit his thoughts to others.

The Graduate School of Medicine of the University of Pennsylvania has been training physicians in the different specialties for about forty years. In 1958, a course in medical writing was presented to a small group of these students as an experiment to determine how well such a course would be received. The response from the students was enthusiastic and there is no doubt but that the graduate student physicians will henceforth demand instruction in this valuable field.

Many of the internes and residents in our hospitals in Delaware are training themselves for a field of specialization. It is important to them that they learn how to properly express their thoughts to others. Practice is an excellent teacher and the State Medical Journal is an excellent medium in which the young physician may gain experience in medical writing. His paper not only will be considered by a group of physicians in regard to the technical content but, if accepted for publication, it will be edited by a professional medical writer. This can be extremely valuable to a beginner who, seeing his own work corrected and rewritten, will gain valuable experience.

There is not a hospital in the state that does not have a number of cases that are worthy of publication in a state journal. It is up to the senior members of each staff to guide the younger men in this important part of their training.

MAJOR MEDICAL MEETINGS IN DELAWARE

Standing Schedule

Beebe Hospital	General Staff	2nd Friday	Monthly
Delaware Hospital	General Staff	2nd Tuesday	Feb., May, Sept., Dec.
Kent General Hospital	General Staff	3rd Tuesday	Monthly
Memorial Hospital (Wilmington)	General Staff	2nd Tuesday	Jan., March, June, Oct.
Milford Memorial Hospital	General Staff	2nd and last Tuesdays	Monthly
Nanticoke Memorial Hospital	General Staff	1st Thursday	Monthly
St. Francis Hospital	General Staff	4th Tuesday 1st Tuesday	March, May, Oct. December
Wilmington General Hospital	General Staff	4th Tuesday	Jan., April, Sept., Nov.

Kent County Medical Society	Monthly Meeting	3rd Tuesday	September - June
New Castle County Medical Society	Monthly Meeting	3rd Tuesday	September - June
Sussex County Medical Society	Monthly Meeting	2nd Thursday	September, June

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Delaware Academy of General Practice	Monthly Meeting	1st Tuesday	September - June
Delaware Pathology Society	Weekly Meeting	Each Friday	

Special Schedule

Medical Society of Delaware	Premature Institute	A. I. du Pont Institute	December 3, 1958
Medical Society of Delaware	Medico-Legal Symposium		February 22, 1959
Medical Society of Delaware	Annual Meeting	Academy of Medicine	October 14-15, 1959
American Medical Association	Annual Meeting	Atlantic City, N. J.	June 8-12, 1959
Delaware Academy of General Practice	Annual Meeting	Kent Manor Inn	December 6, 1958
Delaware Academy of Medicine	Building Dedication	Academy of Medicine	October 14, 1959
Delaware Health Forum	"Headaches"	P. S. du Pont School	November 25, 1958
Delaware Health Forum	"Emotional Development and Disturbances of Childhood"	P. S. du Pont School	February 24, 1959
Delaware Health Forum	"Life Stress and Bodily Disease"	P. S. du Pont School	March 24, 1959

Delaware Division, American Cancer Society	Annual Meeting	October 22, 1959
Delaware Chapter, American Heart Association	Annual Meeting	May 19, 1959
Mental Health Association of Delaware	Annual Meeting	April 30, 1959

The Journal will be pleased to receive notice of major medical meetings in this area for inclusion in this schedule.

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*A Symposium on the Pharmacologic Effects of Dartal on the Liver, Chicago, Searle Research Laboratories, Feb. 7, 1958.

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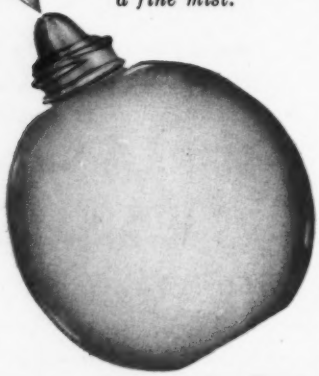

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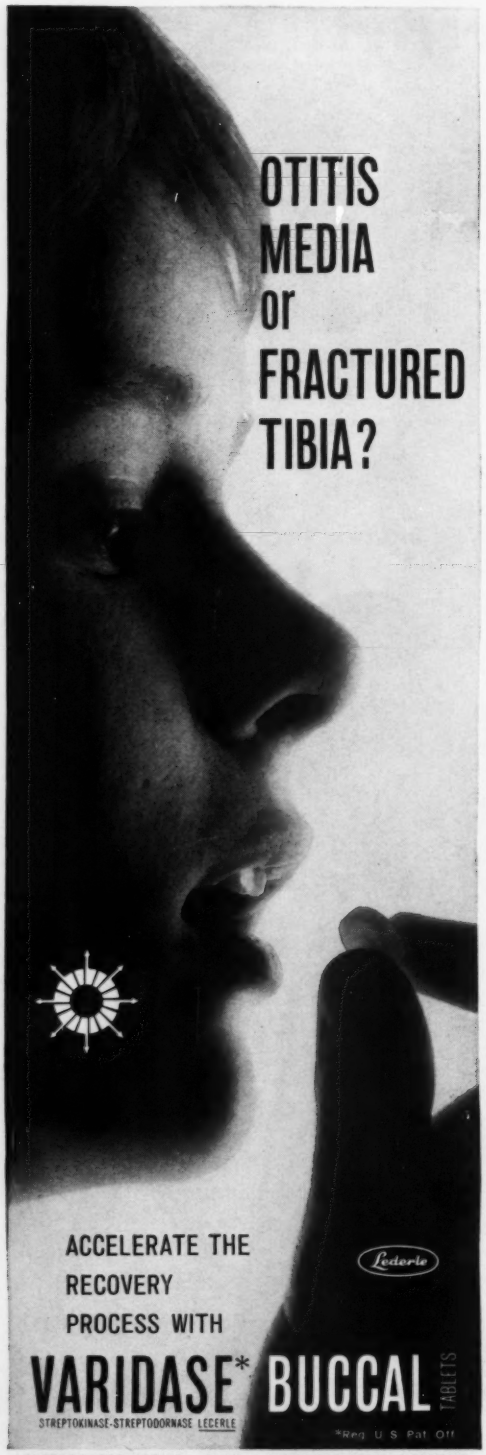

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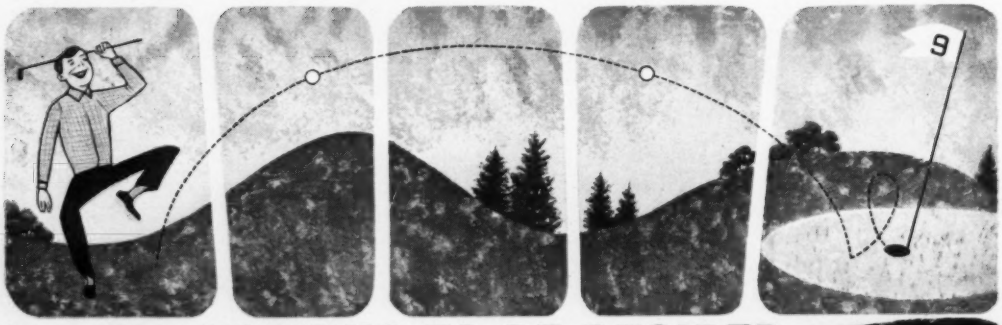

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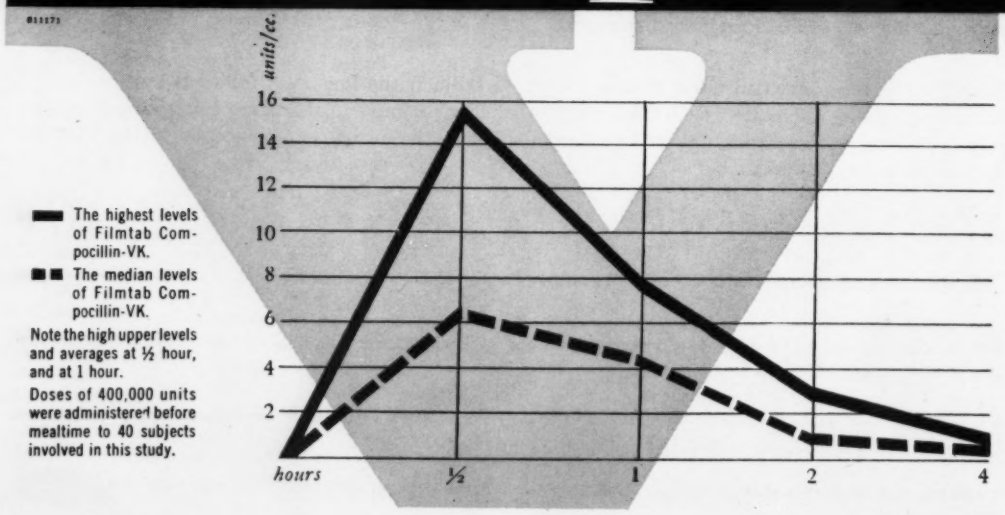

The highest levels of Filmtab Compocillin-VK.

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Note the high upper levels and averages at ½ hour, and at 1 hour.

Doses of 400,000 units were administered before mealtime to 40 subjects involved in this study.

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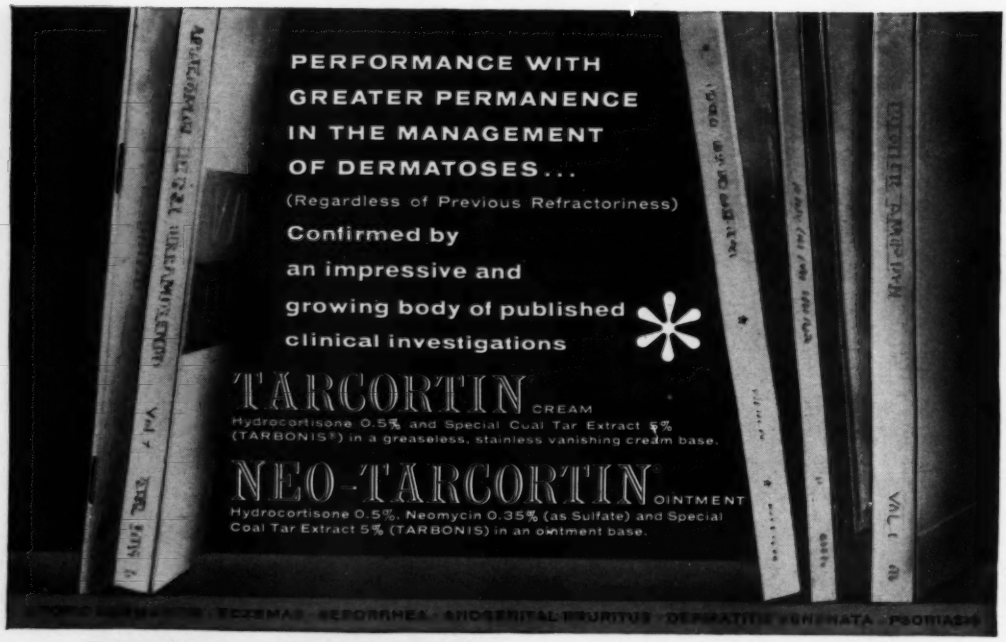
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excellent for lesions of head and hands
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*Finnerty, F. A. Jr.: New York State J. Med. 57:2957 (Sept. 15) 1957.

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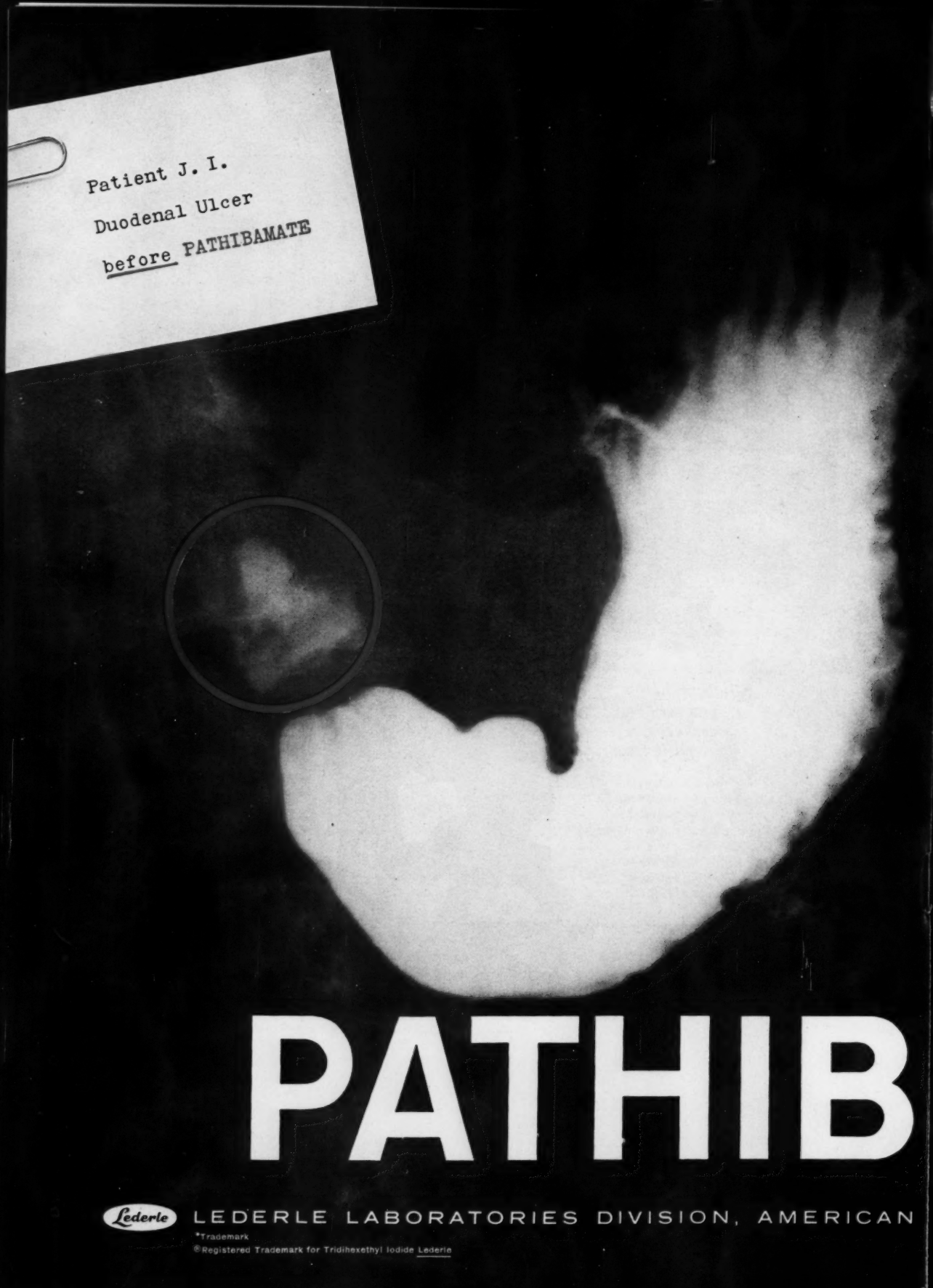
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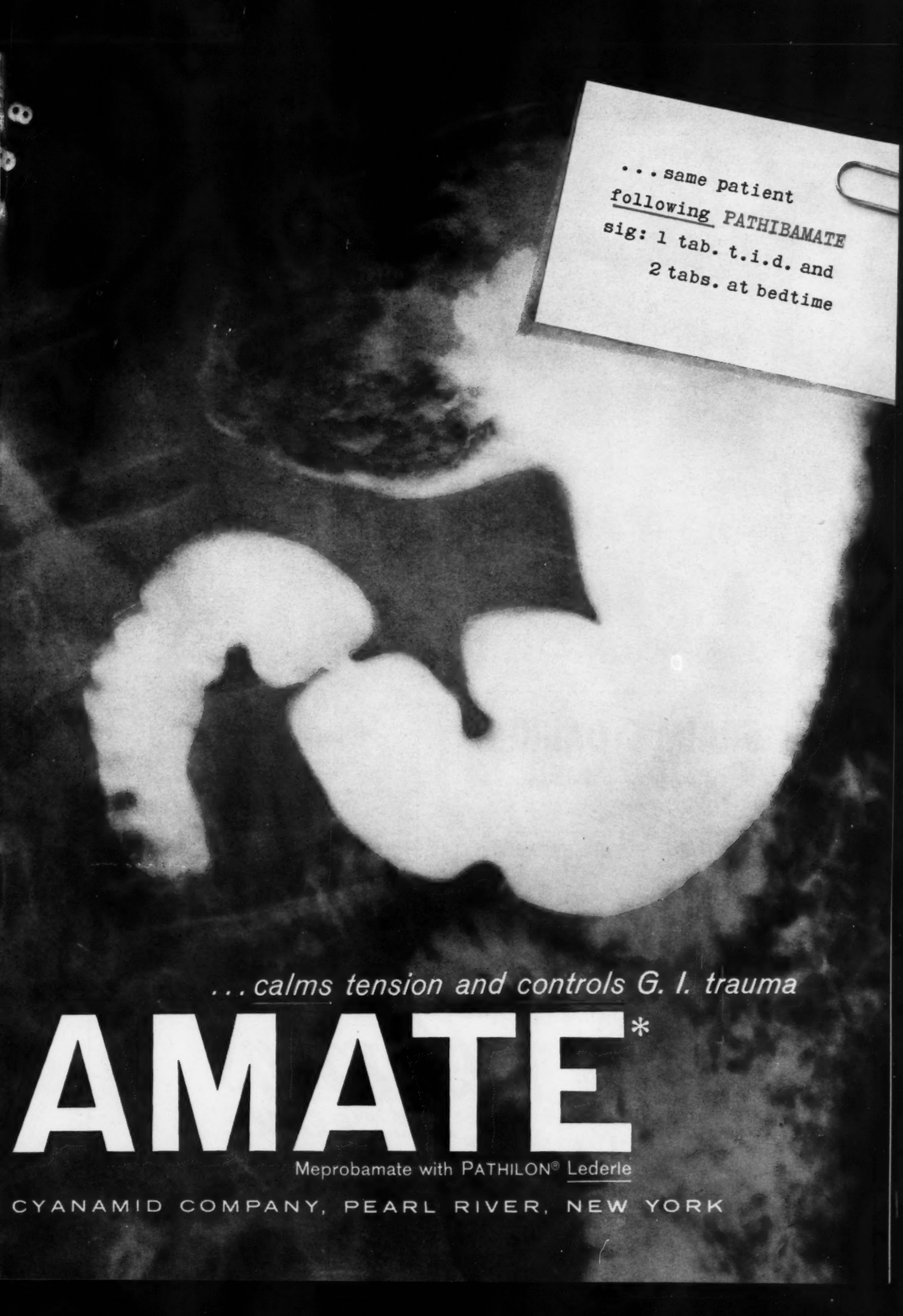

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Each tablet contains:

Aspirin	200 mg. (3 grains)
Phenacetin	150 mg. (2½ grains)
Caffeine	30 mg. (½ grain)
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Average Dose:

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Narcotic blank required.

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q. 12 h.

Two capsules on arising **last all day**
Two capsules at bedtime **last all night**
relieve nervous tension on a *sustained* basis, without between-dose interruption

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1. Meprobamate is more widely prescribed than any other tranquilizer. Source: Independent research organization; name on request.
2. Baird, H. W., III: A comparison of Meprospan (sustained action meprobamate capsule) with other tranquilizing and relaxing agents in children. Submitted for publication, 1958.

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250 mg., 125 mg.

ORAL SUSPENSION
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125 mg. per tsp. (5 cc.), 2 oz. bottle

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antibacterial plus added protection against monilial superinfection

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with iron in the well-tolerated form of ferric pyrophosphate...plus sorbitol for enhanced absorption of both iron and B_{12}.

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Vitamin B_{12} Crystalline	25 mcgm.
Thiamine HCl (B_1)	10 mg.
Pyridoxine HCl (B_6)	5 mg.
Ferric Pyrophosphate (Soluble)	250 mg.
Iron (as Ferric Pyrophosphate)	30 mg.
Sorbitol	3.5 Gm.

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more potent and comprehensive treatment than salicylate alone
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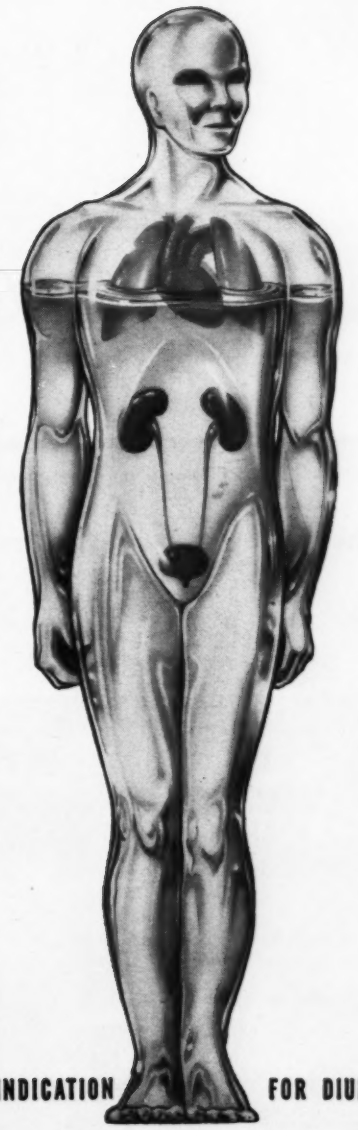

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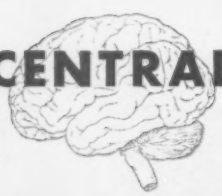

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Neo-Synephrine® hydrochloride	5.0 mg.
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Ammonium chloride	70.0 mg.
Menthol	1.0 mg.
Chloroform	0.02 cc.
Alcohol	8%

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Vitamin B-6	1 mg.
Vitamin B-12 Activity	3 mcg.
Panthenol	5 mg.
Nicotinamide	20 mg.
Folic Acid	0.1 mg.
Biotin	30 mcg.
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Calcium Carbonate	125 mg.
Boron	0.1 mg.
Cobalt	0.1 mg.
Fluorine	0.1 mg.
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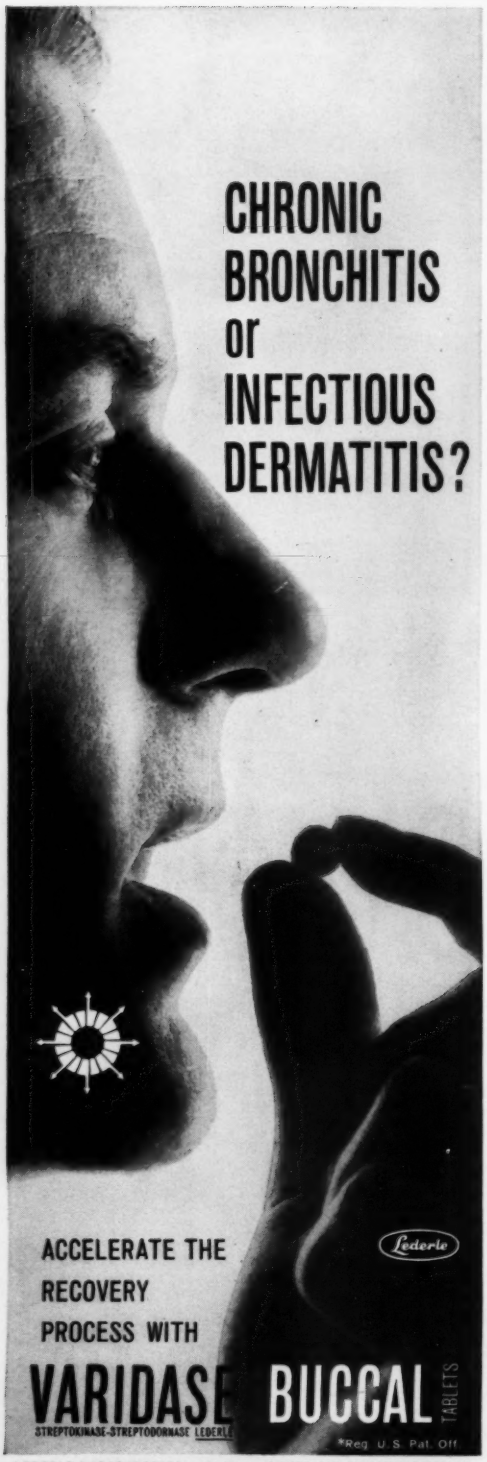

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Source—Lichtenstein, M. E.: GP *16*:114 (Oct.) 1957.

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